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PRIMARY CARCINOMA OF THE LUNG

Bronchiogenic Cancer—A Clinical and Pathological Study

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PRIMARY CARCINOMA OF THE LUNG

I INCIDENCE

A diagnosis of carcinoma originating primarily in the lungs was probably never made by the older clinician, and even the pathologist of the past regarded the disease as a rarity Thus, in 1896, Passler was able to collect only 57 necropsy reports of this condition It is interesting that about fifteen years later, in 1912, Adler compiled from available literature 360 reports The literature of the last decade abounds with articles on this disease, and in Germany alone the number of reported cases of bronchial cancer runs into thousands

Lubarsch (1924) in an investigation on the incidence of cancer in Germany in the years 1920 and 1921 found that of 8301 instances of epithelial malignant tumors, 450 or 5 4 per cent were primarily pulmonary Berblinger noted that in Jena from 1919 to 1924 the disease occurred in 8 3 per cent of all cancers, and Seyfarth found in Leipzig 307 bronchiogenic cancers, which represented 8 per cent of all cancers Ferenczy and Matolczy investigated 62,802 necropsies performed in the pathologic institute of Vienna, and of 6791 cancers, 282, or 4 2 per cent were of bronchial origin Of 36,428 post-mortem examinations performed from 1906 to 1928, Bieberfeld found 207 bronchiogenic cancers, or an average of about 5 5 per cent to all cancers Whal estimated that a little more than 7 per cent of all cancers found in the Moabit (Berlin) Hospital in the last decade were of bronchial origin Sonnenfeld's statistics, including 17,340 necropsies, are to the effect that 10 03 per cent of all cancers are primarily pulmonary Junghanns found 339 bronchial cancers, or 1 67 per cent of all necropsies performed in Dresden from 1893 to 1927 In the period from 1923 to 1927 it occurred in 20 68 per cent of all cancers Kuhn's figures indicate 173 bronchial cancers from 1922 to 1927, representing 5 3 per cent of all cancers

Of considerable interest are figures given by Kikuth whose necropsy material extended over a period of thirty years (1889-1923), including

246 cases According to this author, primary carcinoma of the lungs represented 9 5 per cent of all cancers in the Hamburg-Eppendorf Hospital In 1923 the number of primary pulmonary cancers equaled one-third of the number of carcinomas of the stomach found at necropsies in this large municipal hospital In Prague, Holzer found that in the five years between 1920 and 1924 it occurred in 7 98 per cent of all cases of epithelial malignant disease In the Berlin Pathologic Institute, Hanf stated that 7 5 per cent of all cancers originated primarily in the bronchi

Reports from other German sources (Marchesani, Briese, Materna, and others), although dealing with smaller numbers are not less expressive as to the high incidence of this condition (table 1)

In England, Payfair and Wakeley found only 4 bronchiogenic cancers in 3183 necropsies performed from 1901 to 1923 in the Kings College Hospital Duguid found 175 primary intrathoracic neoplasms in 10,780 necropsies performed at the Manchester Royal Infirmary since 1868 The incidence of the disease in Manchester varied from approximately 1 5 per cent in the last century to 2 5 per cent from 1901 to 1925 The material of the Leeds General Infirmary containing necropsy records for thirty-seven years was investigated and reported in detail by Bonser, who found that on the average this malignant condition occurred in 1 06 per cent of all cancers, and that the highest figure, 1 30 per cent, was noted in the period from 1908 to 1912 Simpson stated that in the London Hospital there are records of 139 cases of bronchiogenic cancers, and that these neoplasms constitute nearly 4 per cent of the total number of carcinomas At the St Bartholmew's Hospital, London, Maxwell investigated 28,227 necropsy reports Of this number, 2181 were malignant tumors, 204 of which arose in the thoracic cavity

In Basle, Switzerland, Staehelin reported that 4 per cent of all malignant epithelial tumors were of bronchiogenic origin In Bern, Probst found that more than 7 per cent of all cancers originated in the lungs

In France, although there are numerous sporadic case reports dealing with this disease, figures concerning its incidence in the larger hospitals are lacking Letulle (1924) found 11 pulmonary cancers in 2560 necropsies, 0 46 per cent, performed in the Hôpital Boucicaut

it occurs in from 2 to 4 to 1000 necropsies

In Florence, Italy, Pekelis found that between 1919 and 1925, in necropsies of patients over 20 years of age, the incidence of cancer in general was 14 1 per cent and that of primary cancer of the lung 0 13 per cent Between 1925 and 1929 the respective incidences were 11 08 per cent and 0 26 per cent

In this country similar numerous articles on this subject were published within the last ten years Barron found 13 bronchiogenic cancers in 4362 necropsies performed from 1899 to 1921 Grove and Kramer reported 21 primary pulmonary tumors in 3659 post-mortem examinations Very high figures were given by Wells, who found 17 bronchiogenic neoplasms in 403 patients Fishberg's report contains 60 bronchiogenic cancers found at the Montefiore Hospital, New York City At the Boston City Hospital, Roshan found that from 1910 to 1928 there were 3004 adult necropsies, of which 314, or 10 4 per cent, were diagnosed as cancer During this period primary carcinoma of the lungs occurred 21 times, or 0 7 per cent of all adult necropsies and 6 69 per cent of all cancers Roshan further stated that from 1910 to 1918 there were 4 cases of bronchiogenic cancer at the Boston City Hospital among 964 necropsies performed on adults, 1 42 per cent, and this increased in the years 1919 to 1928 to 17 cases among 240 necropsies, 0 82 per cent

The statistics quoted from German literature are of particular interest when compared with the figures given by earlier writers Thus, in 12,307 necropsies performed in Breslau from 1854 to 1886, Fuchs found primary carcinoma of the lungs in only 0 065 per cent, Passler found 0 18 per cent among 9246 necropsies performed in Munich from 1881 to 1894

The relative frequency of this condition as seen lately in the necropsy room when compared with the older figures referred to has led observers to the belief that the disease is of "recent" origin and that it is virtually increasing in frequency The increase in the number of bronchiogenic tumors in Hamburg-Eppendorf is illustrated in figure 1 taken from Kikuth (fig 1)

Berblinger, by analysing his material, found that in the years from 1910 to 1914 the condition occurred in 2 2 per cent of all cancers,

from 1915 to 1919 it numbered 2 9 per cent, and from 1919 to 1924 it rose abruptly to 8 3 per cent Similarly, Seyfarth's figures show 5 01 per cent from 1900 to 1906, 6 88 per cent from 1907 to 1913, 11 23 per cent from 1914 to 1918, and 8 75 per cent from 1919 to 1923 Staehelin, too, noticed an increase in the number of necropsies on patients with bronchiogenic cancer thus, from 2 1 per cent seen in the first five years in this century, the number rose to 4 9 per cent in the

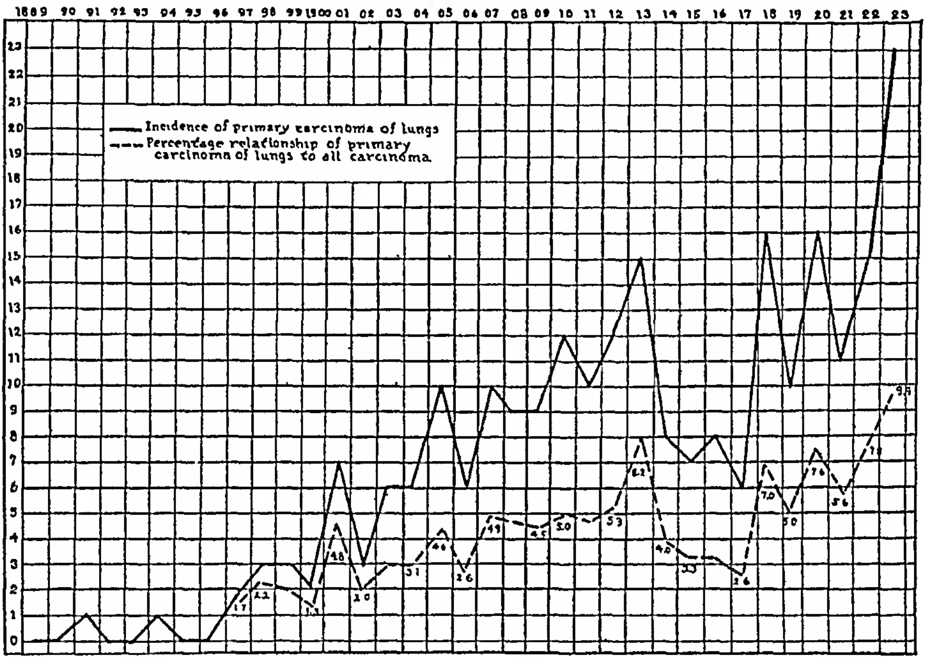

FIG 1 INCREASE IN THE NUMBER OF PRIMARY PULMONARY CANCER IN HAMBURG-EPPENDORF (KIKUTH)

The solid line indicates incidence of primary carcinoma of the lungs, the broken line, the percentage relationship of primary carcinoma of the lungs to all carcinoma

years from 1921 to 1923 The incidence of the disease and the rate of its increase in different clinics are shown in table 1 (pp 379–380)

That primary carcinoma of the lungs is of rather frequent occurrence and not a rare disease is no longer contested by observers The present debate is whether the increase is real or only apparent

The statistical incidence of cancer in general is made up from postmortem examinations, from observations made by surgical exploration, and from reports made by clinicians The reliability of cancer

TABLE 1

Statistical incidence of bronchiogenic cancer

AUTHOR	NUMBER OF CASES	YEARS	PERCENTAGE TO ALL CANCERS	PERCENTAGE TO ALL NECROPSIES
Barron	13	1899–1921		0 3
Bejach	53	1908–1913	4 8	0 45
Berblinger	42	1910–1914	2 2	0 34
		1915–1919	2 9	1 30
		1920–1925	8 3	
Biberfeld	207	1897–1906	2 1	
		1907–1916	6 0	
		1917–1926	6 2	
Breckwoldt	47	1911–1919		
Briese	60	1898–1916	4 5	0 46
Feilchenfeld	22	1895–1900	1 3	0 43
Ferenczy and Matolczy	282	1896–1925	4 20	
Grove and Kramer	21	1917–1924		0 57
Junghanns	339	1893–1897	14 12	1 36
		1898–1902	11 62	0 98
		1903–1907	11 54	1 22
		1908–1912	12 98	1 31
		1912–1917	13 58	1 62
		1918–1922	16 58	1 93
		1923–1927	20 68	2 86
Katz	49	1906–1926	7 74	1 30
Kikuth	246	1889–1899		0 07
		1900–1911	3 8	0 37
		1912–1923	5 8	0 58
Kühn	173	1906–1919	0 74	0 18
		1910–1913	4 10	0 41
		1919–1921	2 97	0 28
		1922–1924	5 32	0 55
		1925–1927	5 29	0 60
Letulle	11	1898–1923		0 47
Lubarsch	450	1920	5 40	
Marchesani	26	1887–1896		0 26
		1896–1906	2 50	0 18
		1906–1916		0 13
		1916–1922		0 30
Materna	19	1910–1922		0 35
Probst	76	1906–1910	0 13	0 11
		1911–1915	3 34	0 38
		1916–1920	6 12	0 59
		1921–1925	7 17	0 97
Redlich	31	1900–1905	6 30	
Rosahn	21	1910–1928	6 69	0 70

TABLE 1—*Concluded*

AUTHOR	NUMBER OF CASES	YEARS	PERCENTAGE TO ALL CANCERS	PERCENTAGE TO ALL NECROPSIES
Schamoni	13	1912–1918	5 30	
Seyfarth (Leipzig)	307	1900–1906	5 10	0 67
		1907–1913	6 88	0 90
		1914–1918	11 23	1 01
		1919–1923	8 75	
Schlesinger (Leipzig)	120	1924–1929	13 54	
Simpson	139		4 00	
Sonnenfeld	178	1909–1914	4 68	0 33
		1915–1919	3 79	0 33
		1920–1924	8 08	0 90
		1925–1929	10 63	1 83
Staehelin	65	1900–1911		0 20
		1912–1914	4 00	0 50
		1915–1923		0 63
Wahl		1910–1914	5 50	
		1915–1919	4 40	
		1920–1924	7 7	

statistics has been the subject of numerous controversial investigations For particulars on this matter the studies by Wilcox, Lubarsch, Wells, Peller, and Menetrier may be consulted The opinion of these writers may be briefly stated

The value of figures as furnished by clinical diagnoses of inaccessible (internal) cancers is contested because of the fact that the margin of error in the clinical diagnoses of inaccessible (internal) cancers is wide Thus, Lubarsch (1924), by investigating the cancer statistics of the German Republic for the years 1920 and 1921, arrived at the conclusion that the errors in diagnoses in the clinical material were so significant (32 44 per cent), that cancer statistics as to incidence and localization of the tumor can have little value Likewise Wells (1923 and 1927) related that in a total of 578 cases of cancer at the Cook County Hospital in Chicago, there were 211 incorrect diagnoses —a diagnostic error of 32 5 per cent "Such a high ratio of incorrect diagnoses in a great hospital," said Wells, "might seem to be evidence of something wrong with the hospital, but we find that other institutions dealing with a similar class of cases, in which most of the cancers coming to necropsy are of the internal organs, exhibit not

dissimilar figures" He quoted Bashford, Reichelmann, Berenczy and Wolf, and Bilz, who in London, Berlin, Budapest and Jena, respectively, reached nearly the same conclusions Wilcox, whose important investigation was published in 1917, and Peller, who reported his studies on the incidence of cancer in 1925, are in accord with the ideas of Lubarsch and Wells

It is significant that parallel with the alleged increase in the occurrence of cancer, there is also a rise in the incidence of other morbid processes, usually termed as "degenerative" diseases Eggers, for instance, found that from 1900 to 1924 inclusive, the mortality incidence from cancer and from degenerative diseases show a regular and even increase He moreover noted that cancer and the combined death rate from the other usual diseases of advanced age show an almost strictly proportionate rate of increase for the twenty-five-year period

Of particular interest is the observation that death due to disease of the heart, and also to arteriosclerosis has markedly increased in the last decade, while that due to diabetes has become very low "Prior to 1914," wrote Joslin, "deaths from coma and diabetes reached 61 per cent, but since August, 1922, have fallen to 20 per cent, and for the last year to 10 per cent Coincidentally, deaths from arteriosclerosis have advanced from 15 to 47 per cent" Joslin attributed this to prolongation of the life of the diabetics, who, with the former methods of treatment, would have died long before their arteries had become "hardened" Joslin further related that "the average age at the death of 339 patients (Joslin's) in the Naunyn period (1898–1914) was 44 8 years, the average age at death of the 607 fatal cases in the present Banting period (since 1920) was 54 2 years, and for the last year 60 fatal cases, the average age was 59 years" Similarly a large part of the population spared from tuberculosis as a result of modern hygienic measures, has reached a more advanced age [illegible] become the prey of an epithelial malignant disease

That the mean length of life is considerably greater [illegible] formerly, and that by far a greater proportion of peo[illegible] advanced age, is accepted by all writers Observations [illegible] effect that twenty years have been added to the av[illegible] human life within the last three or four decades Th[illegible]

ımportance ın connectıon wıth the "cancer age " The increase, then, ın the span of human lıfe for the last few decades ıs a lıkely ımportant factor ın the rıse ın the mortalıty, not only from "degeneratıve" dıseases, but from cancer In fact, the hıgher ıncıdence of epıthelıal malıgnant dısease noted lately concerns ındıvıduals above the ages of 40 and 50, whıle ın the less advanced age-perıod statıstıcs show no changes ın the ıncıdence of thıs condıtıon Indeed, as an observer expressed ıt "We run the danger of growıng old "

It also ıs remarkable that parallel ınvestıgatıons on the ıncıdence of external (accessıble or easıly dıagnostıcated) cancers show no ıncrease (Renaut, Peller, Wells)

TABLE 2

	1901	1920		1901	1920
Cancer of tongue	50	55	Cancer of ıntestıne	190	338
Cancer of uterus	355	321	Cancer of pancreas	48	78
Cancer of vagına and vulva	21	18	Cancer of lungs	15	50
			Cancer of ovarıes	58	78

The above table (table 2) taken from Renaut shows the ıncıdence ın Lausanne of external and vısceral cancers ın the years 1901 and 1920 respectıvely

Hence, ın addıtıon to the prolongatıon of lıfe, the more frequent regıstratıon of vısceral cancers ın recent years result ın all probabılıty from better dıagnostıc methods [1]

Finally, ıt would be mısleadıng to judge of the ıncıdence of cancer from necropsy fındıngs only (as ıt ıs the case ın most ınstances wıth bronchıogenıc cancers) Fırst, the number of performed necropsıes ıs

[1] Wolff, (Karl), ın a recent (1930) crıtıcal study of cancer statıstıcs, emphasızed theır uncertaınty and unrelıabılıty Thus he wrote "Whereas Gusserow has fırmly establıshed by way of statıstıcs that multıparous women are very prone to develop cancer of the cervıx uterı, Kauffmann, on the contrary, found that they are less lıable to contract the dısease " Lıkewıse, Rau, by ınvestıgatıng the materıal of the Dresden Pathologıc Instıtute, has reached the conclusıon that cancer ın the male has ıncreased sınce the World War, whıle Junghanns found from the same materıal that there was a post-war decrease ın the dısease ın man Wolff quoted Rıley to the effect that "statıstıcs are not ıntended to tell the truth " It may also be saıd that they are by no means a substıtute for judgment

insignificant when compared with the number of deaths (5 per cent in Germany, according to Lubarsch) Second, a hospital population does not represent a cross section of a given community

Briefly, then, the virtual incidence of cancer cannot be ascertained at the present

The notion that primary carcinoma of the lung is rapidly increasing has come from post-mortem observations made in the majority of instances by German writers However, Staehelin, basing his conclusions on years of personal observation, is of the opinion that the increase is more apparent than real Breckwold, too, by analysing

TABLE 3

The incidence of bronchiogenic cancer correctly diagnosed in the clinic (Junghanns, modified)

AUTHOR	CITY	YEARS	CORRECT DIAGNOSIS
			per cent
Pässler	Breslau	1881–1894	0 0
Ferenczy and Matolczy	Vienna	1896–1900	5 0
		1917–1925	28 4
		1925	50 0
Junghanns	Dresden	1908–1912	10 0
		1928–1929	48 0
Kikuth	Hamburg	1923	30 0
Lipschitz	Zwikau	1922	0 0
		1925	25 0
		1928	81 3
Schönherr	Chemnitz	1925–1927	37 0
Simpson	London	1907–1925	52 00
Staehelin	Basel	1924	35 0
Zalka	Budapest	1919–1927	26 2

the figures and charts given by Kikuth found that the increase in this disease noted in the Hamburg-Eppendorf Hospital is only apparent He himself, in an investigation of the material of the Hamburg-Barmbeck Hospital, which is about as large as the Hamburg-Eppendorf, and which deals with a similar type of patient, has reached the conclusion that the incidence of primary cancer of the lungs in this hospital has not changed since the opening of the institution in 1913 Hanf, in a work inspired by Lubarsch, recently investigated the incidence of primary pulmonary cancer in the Pathologic Institute of the University of Berlin Like other observers, she noted that the

incidence of this disease is higher now than formerly, but runs parallel with that of other cancers, and this author is of the opinion that the increase is in all probability only apparent Likewise, in England, Bonser, *in the thorough investigation* to which we have referred, arrived at the conclusion that the increase in bronchiogenic cancer is no more than apparent We repeat that not only the former clinician, but the former pathologist considered that bronchiogenic cancer is an exceedingly rare disease

The older clinician was poorly armed with the accessory methods for the diagnosis of pulmonary diseases The tubercle bacillus, which is in reality the single criterion in making the diagnosis of pulmonary tuberculosis certain, was discovered in 1882 The roentgen rays as an effective aid in the diagnosis of diseases of the thoracic cavity, have been applied successfully in the clinic only for the last fifteen years Bronchoscopy is likewise of recent origin, and, the use of iodized oils 40 per cent is as yet in its rudimentary state Surgical exploration in obscure and doubtful cases as practiced in the diagnosis of abdominal or pelvic organs has not been applied to intrathoracic pathologic conditions, since the lungs have been considered from the surgical standpoint as a *noli me tangere* For this reason, neoplastic diseases of the lungs were rarely identified by the older clinician

The older pathologist, too, was confused as to the criteria concerning primary and secondary pulmonary neoplasms The uncertainty was increased by the fact that Virchow, and more recently, Lubarsch (1895), stated that those organs which are frequently the seat of a metastatic involvement by malignant tumors are only in rare instances the seat of a primary new growth The lungs were quoted usually as an example Since from the circulatory point of view these organs are the point of convergence of the body, malignant cells which happen to invade the blood or lymph streams invariably reach the lungs where they form secondary nodules or masses, the latter not infrequently overshadowing that of the primary growth Moreover, the failure of the pathologist to demonstrate grossly a secondary involvement of the lung by tumor is at present not regarded as being conclusive proof of the actual absence of tumor in the lung Numerous investigators have shown that with tumor elsewhere, blastomatous cells (metastatic) can almost always be detected in the lungs

on careful histologic investigation The foregoing has led, then, to the belief that whenever in the presence of a widespread tumor anywhere in the body, a tumor is found in the lungs, the lesion in the latter should be considered as metastatic As a result, not only macroscopically but under the microscope, this condition was diagnosed as a metastasis, as a sarcoma, an endothelioma, or simply as a mediastinal tumor A large percentage of the so called "oat" cell cancers, formerly recorded as intrathoracic mesodermal tumors, have been recognized as bronchiogenic cancers only in recent years (Barnard), the Schneeberger cancer, too, was until recently regarded by many as a lymphosarcoma and the pulmonary condition of the Joachimstahl miners was up to 1929 looked upon as being tuberculous in nature Sikle relates that since the report of Lowy, who was the first to identify the malignant disease of the lungs among the miners, be was able to find 8 bronchiogenic cancers in 10 necropsies among the workers in the Joachimstahl uranium and radium mines

The lack in the past, of knowledge of this condition, plus the unreliability of cancer statistics in general, considerably weakens the statement that bronchiogenic cancer occurs now more frequently than formerly However that may be, as the problem stands, this point is apparently not susceptible of proof one way or another, and, therefore, no sweeping conclusions should be drawn

The author is of the opinion that the more frequent occurrence of this disease in recent years, as compared with older findings, can be explained on the basis of the following factors (1) Improved clinical and pathological methods of diagnosis, (2) Increased attention to this malady (as Goethe has expressed it Man sieht nur was man weiss"), (3) Increase in span of human life (a much greater proportion of people reach the "cancer age")

The increase, then, is very likely more apparent than real

Age incidence The age incidence of bronchiogenic cancer is the same as that of cancer of other organs, for example, between the fifth and the sixth decades Kikuth found 7 patients between the ages of 20 and 29, 18 between the ages of 30 and 39, 49 between 40 and 49, 77 between 50 and 59, 60 between 60 and 69, 30 between 70 and 79, and 5 at 80 and over In 30 of 47 patients analysed by Breckwold, the disease occurred between the ages of 50 and 70

The age incidence in the author's series is indicated in table 4

In a few instances it occurred in younger persons Staehelin, 19 years, Weller, 17 years, Fishberg, 18 years, Derischanoff, 22 years, (Bronchiogenic cancer and exudative tuberculosis), and in children (Steffen, Hirsh), one case in a boy 5 years

TABLE 4

AGE	NUMBER OF CASES
years	
20–29	1
30–39	3
40–49	12
50–59	16
60–69	10
70–79	4
Unknown	1
Total	47

TABLE 5

Bronchiogenic cancer, incidence as to sex

AUTHOR	SEX	
	Male	Female
Adler	209	163
Briese	34	16
Biberfeld	154	53
Ferenczy and Matolczy	204	78
Fried	39	8
Kikuth	159	87
Probst	64	14
Seyfarth	258	49

Sex incidence There is a prevalence of opinion that the male sex is more often affected with this disease than the female Of Adler's 372 cases, 71 9 per cent occurred in men, against 28 1 per cent in women Lubarsch's material indicates an incidence of 8 per cent (to all cancers) in men as compared with 2 57 per cent in women In an analysis of 1087 bronchiogenic cancers, Breckwold found that 807 patients were males and 280 were females In the author's material, 39 cases occurred in the males, and 8 in the females (table 5)

This phenomenon is explained on the basis that the male sex being more exposed to pulmonary diseases in general is likewise more prone to acquire a malignant disease of these organs It may also be due to the fact that in the female sex the genital organs are the more common seat of a cancer The fact that numerically the male population in the hospital exceeds that of the female, is likely also to play a rôle in the uneven distribution of the disease between the two sexes

Incidence as to seat As demonstrated in table 6, the right lung is more frequently the seat of a bronchiogenic cancer than the left This fact is attributed to the anatomic structure and the topographic peculiarities of the right bronchus, which is shorter, wider and more vertical in direction

TABLE 6

Bronchiogenic cancer, incidence as to seat

AUTHOR	SEAT	
	Right	Left
Adler	188	157
Briese	34	20
Biberfeld	154	53
Ferenczy and Matolczy	169	110
Fried	29	18
Kikuth	123	118
Marchesani	12	13
Materna	10	9
Probst	36	40
Sachs	21	18
Seyfarth	258	49

than the left, and therefore more prone to the penetration of foreign bodies and particles leading to irritation and inflammation, resulting in the development of a malignant condition

II ETIOLOGY

It is a commonly accepted fact that to produce an infectious disease in an animal not only the virulence of the germ, and the "dose" of infectious material but the susceptibility of the host, must be taken into consideration Moreover, the susceptibility of an animal to a given species of bacterium not infrequently depends upon the route by which the organism is introduced

The experimental pathologist has only lately begun to realize that an application of some "irritant" is not alone sufficient always to produce malignant disease Not every "irritating" substance will lead to a malignant disease and even "verified" cancerogenous agents will not infrequently fail to excite a particular susceptible structure to participate in the development of a malignant process

Fibiger has demonstrated that only rats that have been fed with the *Spiroptera neoplastica* (*Gongylonema neoplasticum*) will acquire cancer of the stomach, while other spirochetes will cause no malignant disease [2] Similarly, coal tar products will induce in a mouse a cutaneous cancer but not a rectal Again the *Spirotera neoplastica* leads to an epithelial malignant disease while the *Cysticercus Fasciolaris*, the larva of the cat tapeworm *Taenia crassicolis* (Bullock and Curtis), induces as a rule a malignant connective tissue tumor of the liver Likewise in grafting malignant tumors it was observed that whereas the inoculations into the brain, the anterior chamber of the eye, or the muscles will lead in most instances to a vigorous growth of the transplanted neoplasm, and subcutaneous, intravenous and the intraperitoneal grafts will "take" in from 20 to 25 per cent only, and the intracutaneous method will yield still less favorable results Apparently, therefore, the immunobiologic principles which have been investigated in the study of infectious diseases deserve also to be considered in the study of experimental and spontaneous tumors Not only the carcinogenic substance, but the host and the particular organ or structure attacked need to be considered

The belief has been expressed that carcinoma originating primarily in the lungs was exceedingly rare a few decades ago, and that its recent increase is due to factors brought into life in recent years, namely, the influenza which prevailed in the years 1918 and 1919,

[2] Fibiger was the first to induce cancer in rats and mice with the *Gongylonema neoplasticum* which belongs to the group of nematodes and not spirochetes as it was formerly thought The nematode hatches its eggs in an intermediary host—the *Periplaneta americana*, *Periplaneta orientalis* and also *Blatta americana* (species of cockroaches) By feeding rats with infected cockroaches or with their musculature which harbors the parasite Fibiger observed that the larvae of the nematodes free themselves in the gastric cavity of the rodents, and invade the epithelial structure of their fore-stomach (less often of the stomach and occasionally of the tongue) causing chronic inflammation and epithelial proliferation culminating in about 60 per cent of cases in the development of a cancer of these structures

and the inhalation of tar which is now used in painting roads In the discussion on the alleged agents causing bronchiogenic cancer these facts will therefore be considered in some detail Let us first analyze briefly the rôle of bacteria and of parasites in the etiology of cancer of the bronchus

A Bacteria and parasites as causes of bronchiogenic cancer

The rôle of certain bacteria and also of some nematodes and helminths in the genesis of malignant tumors has been demonstrated in many instances (Fibiger, Bullock and Curtis, Ferdinand Blumenthal) It is believed that these organisms are not specific agents causing the disease, but that their effect is that of a toxic chemical nature, acting as an irritant upon the receptive tissue

Although the lungs are constantly exposed to invasion by bacteria, very few micro-organisms have been regarded as factors in the origin of pulmonary cancer The tubercle bacillus which is found in the lungs of almost every person in civilized countries is considered by Ewing as an "irritating" agent causing pathologic changes in the bronchi ultimately leading to cancer Ewing, therefore, believes that the "chief etiologic factor" of bronchiogenic cancer is tuberculosis It is of interest, however, that the occurrence of tuberculosis and of cancer in the same person or in the same organ is rarely seen at necropsy This rarity was emphasized by Rokitansky, who expressed the belief that the two diseases are mutually antagonistic Lubarsch, Reinhart, and Albrecht, in studies of large necropsy material concurred with this observation The problem was reinvestigated by Raymond Pearl, who also arrived at the conclusion that there is an antagonism between the two diseases This author found that

> "In 886 persons of both sexes and races compared who had a great deal of florid, active tuberculosis (acute, ulcerative tuberculosis of the lungs or intestines, tuberculous meningitis, caries of the vertebrae) there were but eleven cases of malignant tumors, or 1 2 per cent of the total number On the other hand in 886 persons with no recorded lesion of tuberculosis at autopsy having the same age, sex and racial distributions, case for case, as the very actively tuberculous, there were 82 cases of malignant tumors, or 9 3 per cent Among the females, both white and colored, there was not a single case of malignant growth in those with much active tuberculosis "

Pearl arrived at the conclusion that "only rarely does an active considerable tuberculosis coexist with a malignant neoplasm in the same individual which is apparently due to a significant antagonism between the two pathologic phenomena which disappears when and if the tuberculous process retrogresses or heals, particularly by the fibrotic route"

The causes for this curious "antagonism" cannot be explained at the present time with certainty It is possibly due to differences in the metabolism of patients with advanced active phthisis

The rôle played by a particular dietary regime in the origin and growth of cancer has been the subject of numerous investigations that have led to contradictory conclusions Whereas some evidence has been produced to show that food lacking in one particular vitamine may occasionally lead to the development of a new growth, it has also been demonstrated that "poor nourishment" will hamper the advance of an already developed cancer and probably will to some degree interfere with the inauguration of a cancer at the very beginning Thus Friedberger and his associates in a series of experiments have shown that the growth of the Jensen rat sarcoma is largely influenced by the quantity and quality of the food supply In their experiments, food poor in calories or in vitamines, whether due to overheating or to an irrational balance of salts, will interfere with the growth of a tumor On the other hand overfeeding will favor a neoplastic proliferation It is possible, then, that in the florid type of tuberculosis the consumption of particular food-stuffs will lead to a condition interfering with the development of a malignant neoplasm, the cells of which, as shown by Warburg, are "voracious" as compared with those of the normal somatic

The rarity of a carcinoma being engrafted on an acute exudative tuberculous process may also be due possibly to the fact that acute tuberculosis causes death of the patient long before an epithelial malignant disease has had time to develop Finally, the "significant antagonism" of the two processes in the same organ may be explained on the following basis In individuals with a chronic productive type of tuberculosis there occurs an active response of tissues by repair, that is by regeneration In these patients with a protracted phthisis the process of regeneration of the epithelial structures may then ultimately develop into a malignant disease If acute exudative tuberculosis

does not bring about the death of the patient before cancer has had time to develop, the reaction of repair or regeneration in these individuals would be so insignificant as to eliminate whatever cancer-producing effect they ordinarily possess

It is of interest in this connection that cancer will at times develop in cases of lupus vulgaris (the tuberculous origin of which is beyond doubt) which show a tendency toward healing, that is regeneration whether by natural means or due to Roentgen rays[3]

The carcinogenic potentialities of syphilis have been observed by clinicians, who noticed that syphilitic lesions of the mouth, and also of the tongue are frequently followed by the development of leukoplakia[4] (metaplasia), which in a number of cases ends in a malignant epithelial tumor The changes caused by the *spirochaeta pallida* in the lungs of adults are still under discussion The supposed specific pulmonary lesions are, however, often complicated by a secondary infection with various pathogenic and saprophytic micro-organisms which are often associated with bronchiectasis and other chronic diseases of the bronchial tree The etiologic factor of Schaudin's spirochete in the genesis of pulmonary cancer therefore, whether as a determining or as a predisposing factor cannot be established with certainty

Other varieties of spirochetes, and nematodes and helminths, whose carcinogenic potentialities for other organs have been established, have never been reported as related to or found in connection with bronchiogenic cancers.

B The rôle of influenza in the genesis of bronchiogenic cancer

Although influenza has been the source of extensive studies the micro-organism which causes it has not been definitely identified The changes in the lungs caused by the supposed pathogenic germ are also matters for discussion This is possibly due to the fact that investigators have studied different stages of the disease One

[3] The antagonism between tuberculosis and cancer was emphasized by [illegible] the rare occurrence of primary pulmonary cancers as compared [illegible] frequent occurrence of pulmonary tuberculosis As shown, [illegible] lungs is not at all a rare condition

[4] Recent investigators are skeptical as to the [illegible] and leukoplakia of the tongue

described the pathologic anatomy of the lungs found in influenzal pneumonia as follows

"With influenzal pneumonia changes in the small bronchi, especially those which do not contain any cartilage in their walls may vary from superficial necrosis of the mucosa to complete destruction of the bronchial wall, so that the bronchus is replaced by a small abscess surrounded by consolidated alveolar tissue Various degrees of injury are inflicted on small bronchi, namely, necrosis penetrating a variable distance into the bronchial wall and occasionally extending to adjacent alevolar tissue, peribronchial hemorrhage or peribronchial pneumonia in a zone encircling the bronchus, presumably due to direct extention of the injurious agent through the bronchial wall and bronchiectasis "

In thirty-eight of ninety patients that died of influenzal pneumonia Askanazy found

"the normal columnar epithelium of the bronchus to be replaced by stratified squamous epithelium, or that there occurred a metaplasia (protoplasia) of the bronchial mucosa "

Winternitz in addition to protoplasia found

"in many cases (he does not indicate the number) epithelial proliferation, invasion of the surrounding pulmonary tissue, and a typical histological picture of an infiltrating malignant epithelial neoplasm "

Cancer of the lungs as emphasized elsewhere in this treatise is bronchiogenic The disease in these organs results from an excessive (pathologic) regeneration of the "basal" cells of the bronchial mucosa In a number of instances the regeneration results in the formation of a layer of stratified squamous epithelium, that is, there occurs a protoplasia of the bronchial mucosa Since in other viscera this particular type of regeneration has been observed to end ultimately in the formation of a cancer in about 30 per cent of instances, it was presumed by some observers that the same pathologic phenomenon would likewise hold true for the lungs These observers have therefore expressed the belief that the alleged increase in pulmonary cancer resulted from the epidemic of influenza of the year 1918–1919

However, those who have investigated clinical material found that a very small number of their patients had influenza or influenzal pneumonia prior to the pulmonary malignant condition Thus, Kikuth by investigating the records of 249 patients that came to necropsy in the period from 1889 to 1923 found a history of influenza preceding the bronchiogenic cancer in 21 cases only Staehelin found that of 67 cases of primary cancer of the lungs 17 had occurred since the middle of 1918, and of these 4 only gave a history of influenza preceding the malignant condition Simpson's material reveals that in 139 necropsies only 5 patients have developed a bronchiogenic cancer following an attack of influenza In the author's material of 47 patients observed since 1918 only 1 gave a history of having had influenza during the epidemic

There also is a disagreement as to whether the alleged increase in this malignant disease began in the period following the epidemic of influenza In 1912, Adler and a few workers of the last two decades of the nineteenth century stated that primary carcinoma of the lung is probably not of rare occurrence but that the disease is overlooked or not reported In more recent years Staehelin noted that in his experience the climax of the raise was in the years 1912, 1913 and 1914 In Seyfarth's material of 307 patients pulmonary neoplasms occurred in 11 23 per cent of all cancers in the period between 1914 and 1918 and in 8 75 per cent between 1919 and 1925

Finally, it is problematic whether an "acute" irritating agent such as the etiologic agent of influenza, can initiate a cancer The opinion is prevalent that only a protracted application of an irritating agent will provoke a malignant tumor Literature contains but few reports where the authors claimed that a malignant epithelial process had been inaugurated by a single application of an irritant Stauffer from Bruno Bloch's service observed the appearance of an ulcus rodens on the cheek in a sixty-six-year old foundry worker thirty days after a burn The patient had had, however, hyperkeratosis and a "precancerous" condition of the skin for a number of years prior to this accident Stauffer is of the opinion that in instances where a cutaneous cancer rapidly follows a single application of a traumatizing agent, the part of the skin in the vicinity of the cancer which has not been subjected to trauma should be investigated, for it is possible

others suggested that tar, gasoline, and other substances used by automobile cars act in all probability as chemical irritants upon the bronchial tree, leading to epithelial malignant disease Kimura claims to have produced pulmonary cancer by injecting tar into the trachea of laboratory animals His experiments should be accepted with reservation, however, since only one rabbit and one guinea pig were used

Smith (1928) by exposing mice to coal tar fumes, to fumes from the exhaust of an automobile, and also by painting the rodents with gasoline for a period of five months, could not produce carcinoma of the lungs in the coal tar series, it occurred once in 26 mice exposed to exhaust, and once in 29 mice painted with gasoline This proportion, according to Smith, is not greater than the laboratory spontaneous occurrence of primary pulmonary cancers ordinarily found in white mice

It is not at all certain that the alleged increase in the incidence of pulmonary cancers coincided with the inauguration of the custom of painting the roads with tar Moreover, in Russia, where the primitively-built roads are not painted by tar, and where the number of automobile vehicles is infinitesimal, Davidoff, Uspensky and others have noted a marked increase in bronchiogenic cancers in the last ten years It would appear, then, that the supposed recent increase in bronchiogenic cancers cannot be regarded as being the result of painting of roads with tar or its products

D Bronchiogenic cancer and trauma

The etiologic relationship between trauma and visceral cancer may briefly be considered here That accidental or surgical trauma of an external organ of structure has been followed by the development of a benign or malignant neoplasm in the traumatized area has been occasionally observed However an etiologic relationship between trauma and cancer of an internal organ has never been satisfactorily established, for it is obvious that in instances when a malignant disease of an internal organ has closely followed a traumatic accident the possibility of the trauma being merely accidental and being superimposed upon an "occult" tumor or on a previously existing precancerous condition (similar to the case of Stauffer) cannot be excluded

Wells and Cannon described an instance when a bronchiogenic cancer

appeared following a trauma of the thorax They believe that there existed an etiological relationship between the two events basing their belief on the facts that (1) a roentgenologic examination of the chest performed just following the occurence of the accident did not reveal any disease in the lungs and (2) the tumor developed in the area where the trauma occurred However the usual negative roentgenologic finding has a very limited value Thus, in my series, two patients suspected of having tumors of the lungs yielded negative roentgenologic results, yet the necropsy, performed shortly after the roentgen ray examination took place, revealed tumors of the bronchi One of these, with atypical signs of an intracranial lesion of about four months duration, was investigated by a competent roentgenologist for the presence of an intrathoracic neoplasm but the lungs were found to be "clear" The necropsy, however, performed a few days later, revealed a small bronchiogenic cancer with metastases The author is very sceptical of any etiologic relationship between single traumatic insults and cancer of the viscera

Comment

The study of the etiology of cancer comprises three distinct phases (1) The extrinsic factor, that is the tissue "injurer" which is brought from without (and possibly also from within), (2) the intrinsic factor, that is the "readiness" of the host to undergo cancerisation, and (3) the intimate mechanism of the transformation of the cell from a physiologic into a pathologic malignant status

Whereas the last two points are not yet understood, the first is thought to be fairly well established Today 'irritation' (the theory expressed for the first time by Virchow) is regarded as an essential factor in the causation of an epithelial malignant condition Chemical, thermal, and physical substances of different kinds and likewise parasites and bacteria are considered as agents playing predisposing roles in the development of a neoplastic disease

It is remarkable, however, that the 'irritation" does not lead abruptly to the development of a malignant disease Experimental and clinical observations have shown that there occurs a rather considerable "pause" or latent period between the time the injury was applied and the appearance of the disease itself Largely because of this fact the factors or agents which have virtually determined the disease cannot be ascertained This holds true particularly in the so called "inaccessible" (internal) cancers

An analysis of the life histories of the 47 patients with bronchiogenic cancers studied by the author failed to point toward any one of the factors referred to as being the probable agent causing the malignant disease In some instances the patients had suffered bronchopulmonary disturbances for a few years prior to the present illness This has been often interpreted as the preceding "chronic irritation" which has led ultimately to a malignant condition It is very likely, however, that in many patients these symptoms were really due to the already existing pulmonary cancer Bronchiogenic cancer usually runs a protracted course, and marked subjective symptoms often appear only when the tumor has attained large dimensions or has been secondarily altered, that is, has undergone degeneration The tumor, then, in its slow and silent advance usually buries with it the particular agent which might have inaugurated its growth,[5] but it is beyond doubt that irritation is as necessary a predisposing factor in the causation of cancer of the lungs as it is in cancer of other organs

Apparently bronchiogenic cancer is merely a part of the entire problem of malignant disease, and its true etiology will not be known until the final solution of the whole problem is at hand

III HISTOGENESIS

A The bronchiogenic origin of pulmonary cancer

Histogenetically, primary cancer of the lung has been divided by previous writers into three groups according to the epithelial units which the lungs have been considered as containing (1) the epithelium lining the bronchi, (2) the epithelial cells which form the mucous glands, and (3) the epithelium said to line the pulmonary alveoli (the air sacs) Microscopically, the classification was based on the following criteria (1) on the type of cells said to resemble those of the matrix, (2) on their arrangement, and (3) on some properties of the cells such as secretion of mucous Some observers have also based their genetic discrimination on the gross appearance of the tumor. Ewing, who classified the tumor into the groups just mentioned, stated that the combination of the clinical history, gross anatomy and

[5] The *Gongylonema neoplasticum* which inaugurates carcinoma of the fore-stomach of the rat could never be found in the more advanced stages of the tumor or in its metastases

histologic structure will furnish a "reasonably certain and acceptable histogenic classification" This, however, cannot be relied upon Those who have studied primary pulmonary cancer are familiar with the protean clinical manifestations of this malignant disease The

FIG 2 CELLULAR POLYMORPHISM OF BRONCHIOGENIC CANCER ENCOUNTERED IN A SINGLE MICROSCOPIC FIELD
Methylene Blue Eosin, × 110

gross anatomy in this condition, as in cancer of other organs, will hardly furnish criteria as to the particular histologic structure which gave origin to the growth Finally, the microscopic features of a fully developed pulmonary tumor will point to its histogenesis in

exceptional cases only, the morphology of the neoplastic cells varies from one tumor to another (columnar, cuboidal, spindle-shaped, so-called "oat" cells, squamous epithelial cells, basal cells), and even in the same tumor their form frequently varies from area to area (fig 2) On the contrary the arrangement of the cells is rather uniform, in most instances being that of adenocarcinoma

The difficulties in the genetic tracing of a primary pulmonary cancer can be illustrated by the fact that most observers are critical as to the existence of tumors having their origin in the alveolar cell, while others (Letulle) do not include in their classification tumors originating in the mucous glands

Of particular interest are blastomas said to originate from the cells lining the pulmonary alveoli (so-called respiratory epithelium)

Cancer originating from cells lining the alveolar wall Passler (1896) was the first to give a comprehensive discussion of the question and also to review 54 cases of primary cancer of the lung which he found at that period in the literature He reached the conclusion that of this number 47 originated, in all probability, in the bronchial mucosa, while in the others, the histogenesis could not be established He stated, moreover, that cancers having their origin in the pulmonary parenchyma are unknown, or at least that the nonparticipation of the bronchial epithelium in these cases could not be excluded Domeny (1902) thought that tumors made up of small and large nodules composed of small polymorphic cells forming "pearls" are of alveolar origin Other pathologists claimed that squamous epithelial tumors usually originate in the alveolar cells (Beitzke)

In 1912, Adler published his monograph containing a critical review of 374 cases of primary carcinoma of the lungs He wrote "It is now held that carcinoma starting from the pulmonary alveoli is extremely rare, and some go so far as to deny its existence altogether" Adler himself was of the opinion that the great majority of primary carcinomas of the lungs develop from the bronchi, and that a cancer of the lung is, strictly speaking, a bronchial carcinoma Nevertheless, he admitted the existence of alveolar cell tumors which are built up "not of flat but of cylindrical epithelium" More recent observers state that in instances when the alveolar septums are lined by neoplastic cells forming papillary projections the tumor has originated in

the "respiratory epithelium" (fig 3) However, this criterion, too, is erroneous primary pulmonary cancer often metastasizes to other parts of the same lung and also to the other lung by way of the bronchi (bronchial emboli), in which case the neoplastic cells invading the alveoli line their walls in a syncytial manner The author's experimental and clinical studies in this matter have led him to the conclusion that the walls of the alveoli are virtually "naked" and that the cells found in groups along the septums of the air sacs are not epithelial

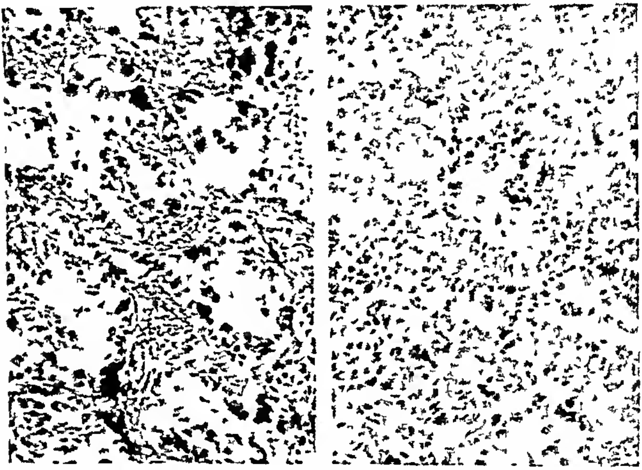

FIG 3 THE LINING OF THE WALL OF THE AIR SACS BY NEOPLASTIC CELLS IN BRONCHIOGENIC CANCER

but mesenchymal in origin (figs 4 and 5) and consequently could not be expected to produce carcinoma The matter may be briefly restated

Experiments by previous workers have shown that when vital dyes in solutions are introduced into the blood stream of animals they are instantaneously picked up (phagocytosed) by one variety of cells in a specific manner, being deposited in the cellular cytoplasm as fine and coarse granules Likewise, certain lipoids (cholesterol, olive oil) introduced *per os* or paren-

terally are attacked essentially by the same large phagocytic cells—the macrophages which dispose of this substance in a way similar to that of the dye Interesting features in this process are the prompt morphologic changes and the rapid proliferation of these cells

I have observed that after the injection of oils and dyes, respectively, into the lungs of rabbits or cats by way of the trachea, the cells found along the wall of the air sacs respond in exactly the way the macrophage does

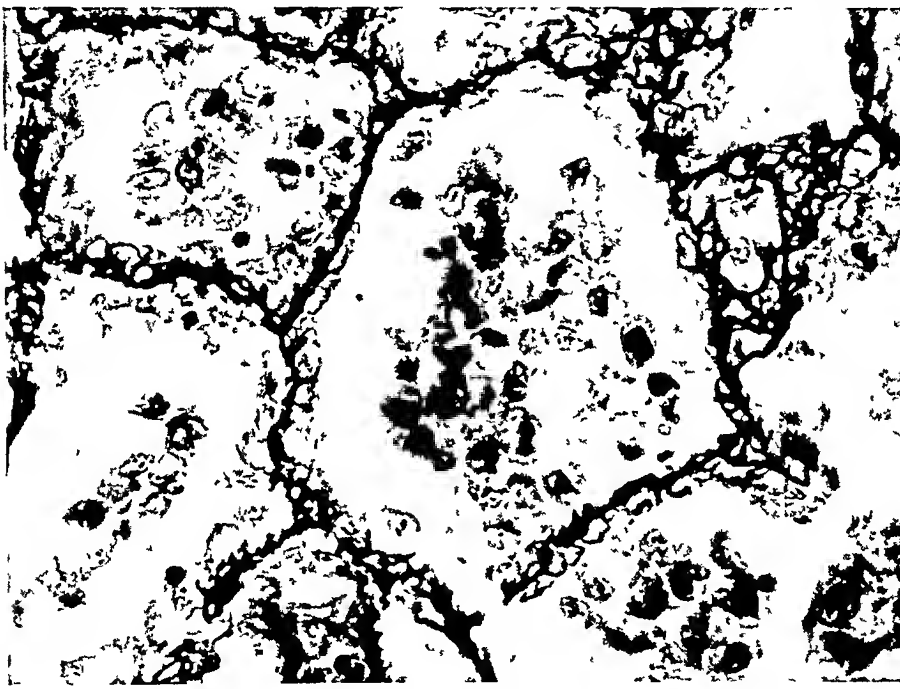

FIG 4 A SECTION FROM A CAT'S LUNG FOLLOWING INTRATRACHEAL INJECTION OF COD LIVER OIL

Free macrophages fill the alveoli "Ghosts" of the same cells are seen here and there alongside the septa Perdrau's method, × 600

elsewhere in the body, that is, by instantaneous proliferation and also by phagocytosis of these substances

Further experiments were conducted with the anthrax bacillus, an emulsion of which in physiologic solution of sodium chloride was injected into the animal's lungs by way of the trachea This microorganism was chosen because of the ease with which it can be demonstrated in tissues and, what is more important, because it is infallibly pathogenic to laboratory animals The experiments have shown that the intratracheal route of infection causes

no disease, provided the extrapulmonary tissues of the animal are spared contamination. Investigation of tissues from the rabbits so infected has disclosed that the pathogenic microorganism is retained in the pulmonary tissue and is destroyed *in situ* within a short time after the injection. As

FIG. 5. A PHOTOMICROGRAPH FROM A DRAWING FROM A SEGMENT OF A CAT'S LUNG FOLLOWING INTRATRACHEAL INJECTION OF COD LIVER OIL

The cells alongside the septum and those lying free in the alveoli are identical, both being macrophages. For comparison, a macrophage from the wall of the splenic sinus is inserted in the right lower corner.

in the previous experiments with the vital dye and with the oil (which should be regarded as "model infections"), the bacillus is instantaneously attacked and phagocytosed by the local macrophages located within the pulmonary septums, and also by those "lining" the wall of the air sacs.

Since the tubercle bacillus is known to be the prey of the monocyte par

excellence, it was thought of interest to study the behavior of these cells (the alveolar "epithelial") in the presence of the acid fast bacillus For that purpose rabbits were infected with Koch's bacillus by way of the blood stream and by way of the trachea respectively, each rabbit receiving

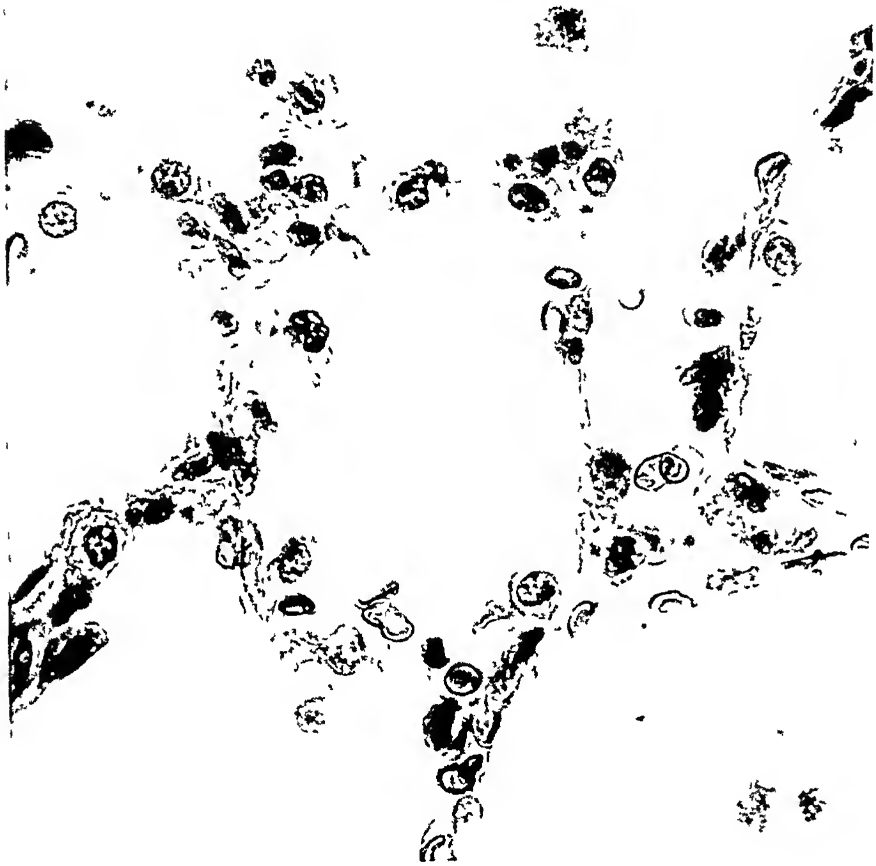

FIG 6 INFECTION OF RABBITS WITH TUBERCLE BACILLI BY WAY OF THE TRACHEA

Under the influence of the acid fast bacillus the alveolar "epithelial" cells have increased in size taking the aspect of large mononuclear phagocytes Some of them are seen as wandering macrophages Methylene-blue-eosin, × 850

one half a milligram of bovine tubercle bacilli emulsified in a physiologic solution of sodium chloride The animals were killed at intervals of from one minute to several weeks after the infection and their tissue studied

As in the previous experiments, the essential reaction to the Koch's bacillus was that of the alveolar "epithelium" Indeed, when the lungs

were examined one minute after the intratracheal injection of the bacilli there had occurred already a metamorphosis of these cells into large cells, with a foamy cytoplasm so characteristic of the macrophage (fig 6) There occurred also an amazing proliferation of these elements, and many of them detached themselves from the alveolar wall to participate in the

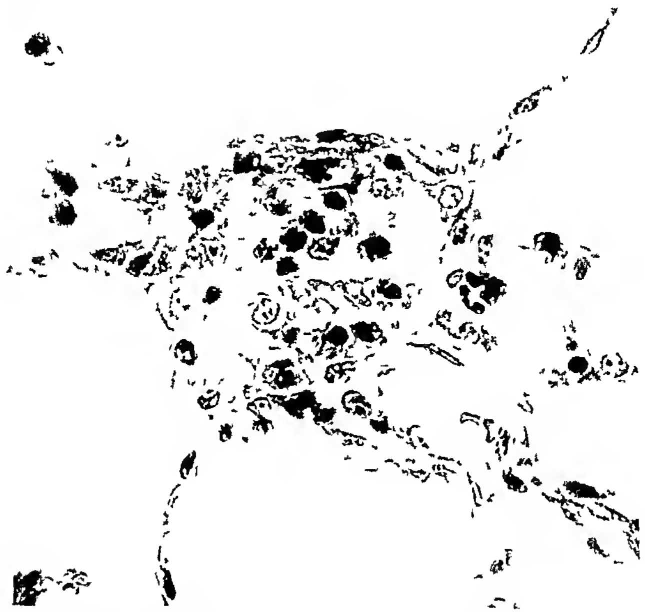

Fig 7 Infection of Rabbits with Tubercle Bacilli by Way of the Trachea
Showing a "primitive tubercle" formed by the alveolar "epithelial" cells 10 minutes after the injection of the acid fast bacilli Methylene blue eosin, × 850

intraalveolar exudate They also showed phagocytosis *en masse* of the tubercle bacilli Within from five to ten minutes after the infection "primitive tubercles" could be found scattered over the sections formed by the alveolar "epithelial" cells (fig 7) It has been observed also that the alveolar "epithelial" cells take part in the extrahepatic formation of bile

The interpretation of the results obtained is obviously open to objection on embryologic grounds Embryology teaches that the air sacs of the embryo are lined with a single layer of cuboidal epithelial cells It is assumed that as a result of the first respiratory effort certain of these cells become flattened and some lose their nuclei altogether, thus leading to the formation of the *anucleated plate-like cells* of the functioning alveolus

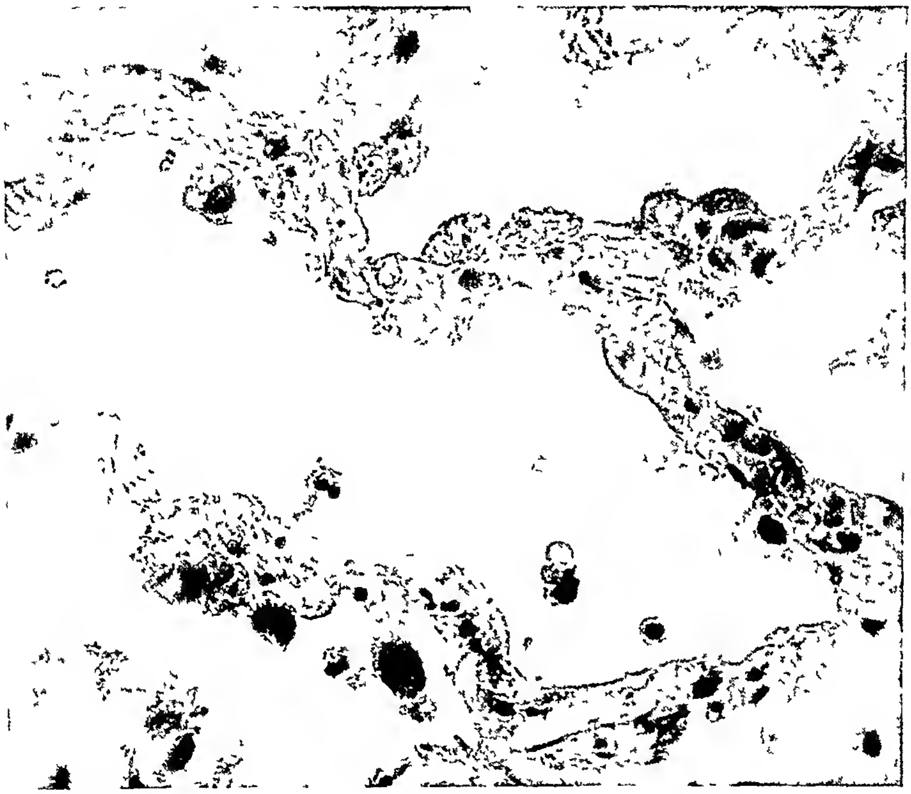

FIG 8 TO SHOW THAT THE WALL OF AIR SAC IS VIRTUALLY "NAKED"
The few cells found in groups alongside the septum display characteristics proper to mesodermal cells (macrophages or histiocytes) Human lung Methylene-blue-eosin, × 600

However, recent investigations of the fetal lung revealed that there exists much uncertainty among investigators as to the embryology of the primordium of the air sacs Thus, Rose, in a study performed in Professor Oertel's Pathologic Institute at McGill University, reached the conclusion that the lungs have a double origin endodermal for the bronchi, and mesodermal for the alveolo-capillary structures Developmentally, according to

this author, the bronchi invade a layer of mesoderm, the cells of which form the capillary system and the cells of the septums Maximow in his *Textbook of Histology* is as yet undecided, urging "a thorough embryological investigation of the lungs in the later stages of intrauterine life," while Policard

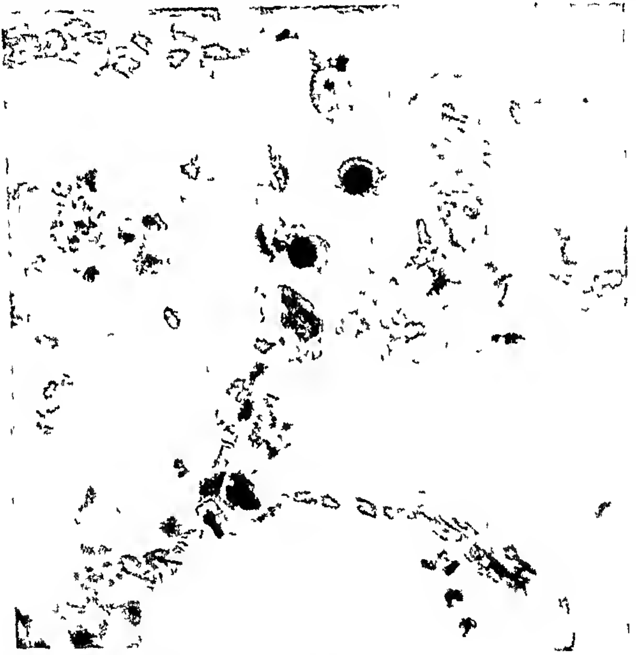

FIG 9 A PHOTOMICROGRAPH FROM A SEGMENT TO A HUMAN PULMONARY ALVEOLUS
The polymorphism of the cells lining the septum must be noted The similarity between the fixed second cell (from above) and the free cell to its right (the exudate) is noteworthy Methylene blue eosin, × 700

and Chiodi believe that originally cuboidal epithelium lines the air sacs but disappears in the later stages of fetal life, to be replaced by mesenchymal cells

Investigation made on adult human lungs likewise shows that the air sacs are in all probability "lined" not by epithelial cells but by

macrophages scattered in groups along the alveolar walls (figs 8 and 9) Since these cells are mesenchymal in origin they therefore could not give rise to an epithelial malignant disease If one therefore excludes the alveoli as a possible source of carcinoma, there remain to be considered the mucous glands and the bronchi

Cancer originating from the mucous glands The mucous glands are structures that lie underneath the bronchial *membrana basalis* Indeed, being made up of epithelial cells, they are considered as being liable to transformation into an epithelial malignant new growth However, Letulle did not include such a variety of tumors in his classification, and, the few cases reported in literature which holds that the condition was believed to have originated from these units are wholly unconvincing No one has ever observed an early cancer of this kind, and the criteria, such as the glandular structure as well as the presence of mucous, which are supposedly characteristic of these neoplasms, in reality distinguish a great many tumors originating from organs that normally form no mucous material Finally, the cells of which the glands are made up are fully differentiated and "apotent" thus being unable to regenerate and undergo a malignant metamorphosis This will be discussed shortly

The foregoing clinical, pathologic and experimental observations point toward the conception that primary carcinoma of the lungs is only bronchiogenic in origin

B Regeneration of bronchial epithelium and pulmonary cancer

The causal and formal genesis of cancer in general and that of the lungs is a matter of dispute Apparently a malignant disease in the lungs results from the "cancerization" of the somatic cell, probably in several ways First, individual cells may acquire the disease, leading to their anarchic growth Second, a local malignant condition may possibly be due to a systemic bodily imbalance of some kind It is, moreover, probable that both conditions are required for the development of the malady, but many observers are still uncertain whether a fully differentiated epithelial cell is liable to become cancerous

It is well established that one of the factors leading to the development of a cancer is chronic inflammation, namely, irritation which

causes degeneration of cells eventually followed by an excessive regeneration However, in the lungs the columnar epithelial cells lining the bronchi have never been observed in a state of regeneration as evidenced by mitoses and proliferation

Ribbert was probably the first to emphasize the fact that neoplasms originate usually from cells which are not fully differentiated, other pathologists stated that in every organ there exist "embryonal centers"

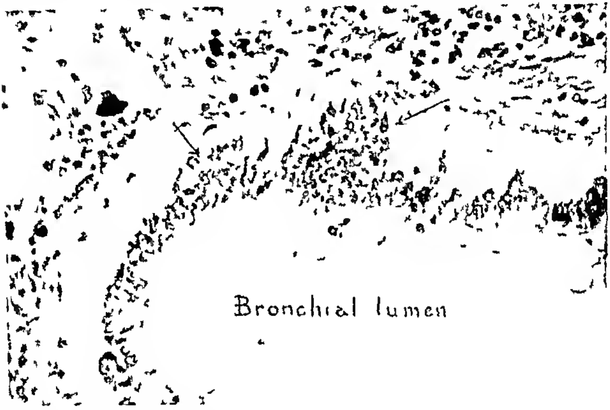

FIG 10 A PHOTOMICROGRAPH FROM A HUMAN BRONCHUS SHOWING THE EARLY STAGE OF BASAL CELL PROLIFERATION

The peribronchial tissue shows signs of inflammation The bronchial mucosa is detached from the basal membrane, which is edematous, being invaded by small lymphocytes The cellular agglomerations indicated by arrows are regarded as the beginning stage of protoplasia (metaplasia)

(physiologic centers of proliferation) which serve as a point of departure for tumors The problem is complicated in that with the methods of observation at the present time the actual metamorphosis of a somatic cell into a malignant cell has never been observed The skepticism is therefore based on the observations (1) that a fully differentiated cell is generally "apotent," and (2) that regeneration, which is a forerunner of a malignant condition, is performed in most instances by cells other than those which appear at first glance to be

affected by the noxious agent The skin is an interesting example in this respect In the presence of damage to this structure, regeneration of the cutaneous tissue will occur by virtue of the basal cells only, which are probably postembryonic undifferentiated cells, but when these cells, too, have been damaged, a skin graft is required for the repair of the defect

The lining of the bronchi and their divisions is made up of three different types of cells columnar ciliated cells, goblet cells, and basal cells—a variety of small oval cells having a narrow cytoplasm and a nucleus rich in chromatin The last mentioned cells lie close to the basal membrane, they do not form the uninterrupted syncytium observed in the skin, but are irregularly scattered forming cellular agglomerations (fig 10) Observation reveals that in the respiratory tract the process of regeneration takes place by virtue of these "basal" cells, which are endowed apparently with latent developmental potentialities

In chronic bronchopulmonary diseases accompanied by damage of the bronchial epithelium, one often notices that instead of the ciliated epithelium there appear cuboidal cells superimposed by many layers of "transitional" epithelial cells which have originated from the preexisting "basal" cells Likewise, in inflammatory processes the cells lining the smaller bronchioles have a tendency to invade the surrounding granulation tissue forming tubular structures (fig 11) This was erroneously described as pulmonary alveoli lined by alveolar wall cells which had "reclaimed" their embryonic cuboidal aspect ("regressive metaplasia") (fig 12) The epithelium of the proliferated bronchioles also not infrequently invades tuberculous cavities lining their walls where they ultimately become cancerous (It is also possible that the cancerous transformation peceded the invasion of the cavity) Askanazy described an instance in which the "basal" cells proliferated to such a degree as to invade the bronchial mucous gland I have observed the same picture in man and also in experiments on cats and rabbits with the intratracheal injection of oils In all instances, when the ciliated columnar cells were destroyed or damaged, the "basal" cells showed only active regeneration (mitoses and proliferation), they formed many layers of small cuboidal or "oat"-shaped cells and also invaded the peribronchial alveoli

Experimental and clinical investigations show that cancer is always preceded by a process of regeneration The development of epithelioma in areas subjected to roentgen rays, the occurrence of epithelioma of the lip in those who smoke pipes, and tar and paraffin cancers are widely known Observation has shown that cancer of the lungs,

FIG 11 SHOWING INVASION OF THE GRANULATION TISSUE BY THE BASAL CELLS OF THE BRONCHUS

too, usually follows a long-standing chronic inflammation Ewing for instance, expressed the belief that the chief etiologic factor of carcinoma of the lungs is tuberculosis, other observers have found it in patients with bronchiectasis, and with pulmonary syphilis Tuberculosis, syphilis and other long-standing pathogenic infections of the lungs, such as chronic inflammatory processes, cause damage of the

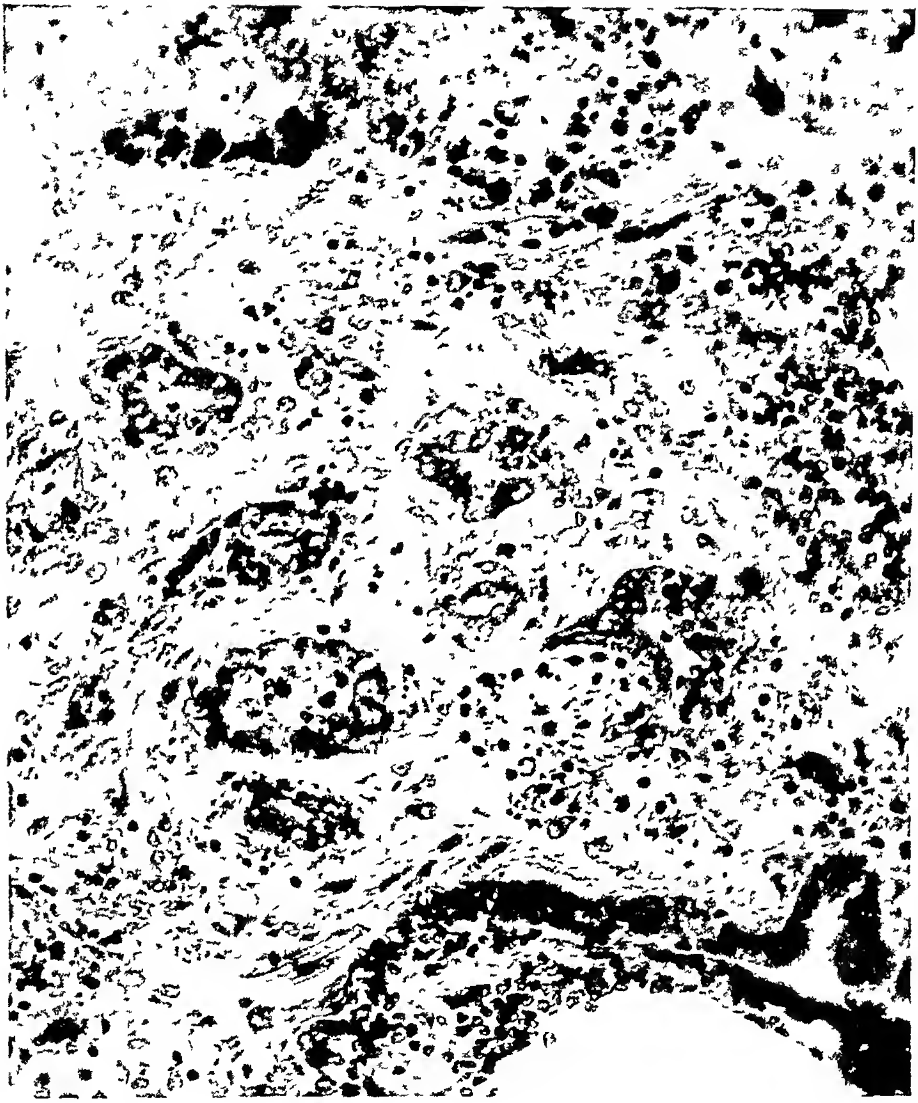

FIG 12 SHOWING NEW FORMATION OF BRONCHIOLAR-LIKE STRUCTURES IN AN AREA OF YOUNG GRANULATION TISSUE, IN A CASE OF INFLUENZAL PNEUMONIA

This condition in a sclerosed lung is a counterpart of what one observes in atrophic (Laennec's) cirrhosis of the liver where new bile ducts are formed in the connective tissue which surrounds the hepatic lobules The glandular structures demonstrated in this photomicrograph were interpreted by older pathologist as "pulmonary alveoli" in which the flat respiratory epithelium has "reclaimed" its fetal cuboidal aspect Hematoxylin and eosin × 300 Figures 12 13, 54, 55, 56 57 and 60 are from patients studied at the Beth Israel Hospital, Boston through the courtesy of Dr Harry Linenthal and Dr M J Schlesinger

bronchial mucosa followed by excessive (pathologic) regeneration which eventually leads to the development of an epithelial malignant disease

The apparent lack of any activity in the process of bronchial repair on the part of the ciliated columnar epithelium in the presence of an active "basal" cell proliferation leads the author to favor the conception that only the latter cells are concerned in the genesis of an epithelial malignant disease in the lungs

C Metaplasia and pulmonary cancer

Post-mortem material reveals that a large percentage of all pulmonary tumors are of the basal or squamous cell type Since normally such cells are absent in the lungs, the origin of these tumors was said to be due to a conversion of the ciliated columnar cells into the squamous epithelial variety The condition is therefore designated as metaplasia (fig 13) This conception of a direct transformation of one "well characterized tissue into another equally well characterized but morphologically and functionally different" was advanced for the first time by Virchow Such hypothesis, however, is not borne out by close observation In the first place, as already noted, it is improbable that the "apotent" ciliated columnar epithelium is able to transform itself into any other variety of cell Another point was raised by Wells (1929), who said

"The formation of metaplastic squamous epithelium brings forward two puzzling topics, one chemical, the other embryologic The chemical peculiarity is that squamous epithelium is characterized by the formation of keratin, which is a definite chemical compound, formed normally, as far as is known, by the cells of ectodermal origin, including the neurokeratin of the central nervous system When cells of endodermal origin, such as those lining the renal pelvis or the uterus, take on the function of forming this peculiar, insoluble, sulphur rich, indigestible, protective chemical, keratin, they have assumed a chemical function which seems to be far removed from their normal capacity Hence we must conclude that metaplasia involves not only a morphologic but a chemical transformation of cells

"For tumor pathology, another problem arises When cells assume the proliferative activity that is characteristic of malignant disease, they usually

lose their more recently acquired functions and retake chiefly the simple vegetative function of proliferation But when a transitional or columnar epithelial surface becomes squamous through metaplasia, and the same protracted irritation that produced the metaplasia continues until cancer results, we find that the newly acquired property of forming keratin has become fixed and the cancer is a keratinizing, squamous cell carcinoma One would expect the epithelium to approach its original, simpler embryonal character, rather than exhibit and return so profound and recently acquired an alteration as the production of keratin "

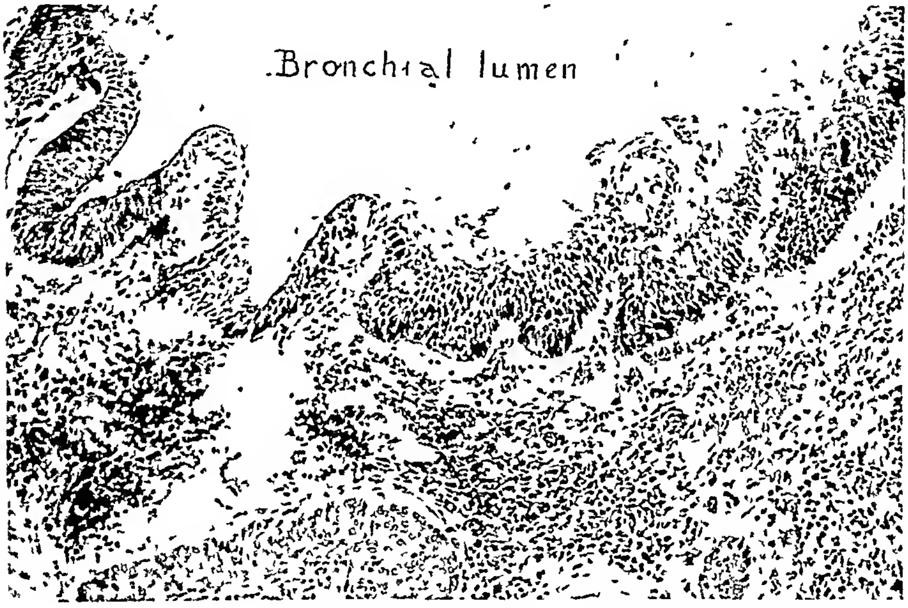

FIG 13 METAPLASIA (PROTOPLASIA) OF BRONCHIAL EPITHELIUM IN A HUMAN LUNG
The bronchial mucosa is made up of a layer of cells closely resembling those of the skin The membrana basalis is dissociated and largely obliterated The tissue between the cartilaginous plates and the basal membrane is edematous, it contains newly formed blood spaces, and is heavily infiltrated with plasma cells and lymphocytes Hematoxylin and eosin, × 110

Today the original conception of Virchow of a direct metaplasia has received a new interpretation Observers emphatically deny the authenticity of a direct transformation of the endodermal columnar cell into an ectodermal squamous epithelial cell Borst, for instance, stated that there is no such thing as direct metaplasia with the persistence of cells, and other workers affirmed that only those cells which

are endowed with "dormant" developmental potentialities may undergo new changes Those cells, however, which have become entirely "apotent" do not regenerate and become still less transformed into a new cellular type Most pathologists regard the so-called metaplasia as a complicated biologic process of regeneration with new formation of cells (neoplastic phase) which is ultimately followed by a differentiation (metaplastic phase) Cells with embryonic or postembryonic potentialities are liable to such a metamorphosis, whereas the ciliated columnar epithelium lining the bronchi is a fully differentiated and therefore a "nonreversible" cell What then, is the origin in the lung of the "foreign" squamous epithelial cells?

The idea of a few observers that this cell is apparently an embryonic rest could not be corroborated by most diligent investigators Clinicopathologic and experimental studies convincingly point to another source It would appear that the "basal" cells already referred to, which lie close to the *membrana basalis* of the bronchus, are the progenitors of the stratified squamous epithelium (fig 14)

Teutschlander observed the process of "transformation" of this cell in the bronchi of rats that died of bronchopneumonia, Goldzicher found it in the lungs of children who died of diphtheria and measles, and Askanazy outlined this pathologic phenomenon in the lungs of persons who died of pneumonia following influenza

Of interest are the experimental studies by Wolbach on changes in the tissues following deprivation of fat-soluble vitamin A By feeding rats a deficient diet, he noticed that the "missing factor" caused a widespread keratinization of epithelium In the respiratory tract the process began in numerous foci, and the rate of the cellular growth was rapid, as attested by numerous mitoses of the basal cells What is more, these experiments have shown that the basal cells begin to proliferate even before any changes are detectable in the columnar epithelium, which only subsequently degenerates and separates from the basal membrane It is also interesting that this process is not necessarily brought forward by a previous inflammation, a mere stimulus generated by a "missing factor" from the food causes an "alarm" among the cells, followed by their multiplication and differentiation

Apparently this pathologic phenomenon occurs in numerous cases of bronchopulmonary disease Above I have quoted Askanazy and Goldzieher who found metaplasia in a high percentage of patients

Fig 14 Metaplasia (Protoplasia) of Bronchial Epithelium in Human Lung

The ciliated columnar epithelium is pushed away by the "basal" cells, which are agglomerated in masses The columnar epithelium shows no signs of regeneration, as evidenced by mitoses and proliferation

who died of pneumonia following influenza and in patients with measles and diphtheria In a recent study, Lawrence Smith (1927) also observed metaplasia in children with whooping cough Examples

of this condition have recently been observed by the author to occur in a great variety of pulmonary diseases

The peculiar character of the differentiation of these cells into squamous epithelium is interpreted in the light of the ontogenesis of the tissue in question From an embryologic standpoint the tracheobronchial tree and the esophagus represent two sister organs, and their development goes parallel Schridde has produced evidence to show that in the earliest stages of development the esophagus is lined with one layer of cuboidal cells, which at the fifth week becomes double and at the tenth acquires goblet cells and ciliated columnar epithelial cells Whereas in the bronchi the development ends at this phase, in the esophagus these cells degenerate and desquamate, being subsequently replaced by a transitional epithelium and finally by a stratified squamous epithelium It is assumed, then, that in pathologic processes the bronchus, in its regenerative attempt, merely reaches in adult age the stage which the esophagus has attained as an embryo

It will be seen, therefore, that the process is not a transformation of the adult columnar epithelium into a squamous type, but that a development of undifferentiated cells followed by proliferation and differentiation occurs The phenomenon is consequently not that of metaplasia, but is one of protoplasia (indirect metaplasia) Briefly, then, the process of repair or regeneration in the bronchi is performed by the bronchial "basal" cell only In physiologic repair, these cells differentiate merely into the normal lining of the bronchus But when the process is pathologic, their fate depends in all probability on the nature of the stimulus and also upon the "resistance" of the host Thus, they may differentiate into metaplastic islands and so remain indefinitely, or they may develop into a malignant condition In fact, most pathologists regard the phenomenon of metaplasia as being a precancerous stage

Summary

1 Carcinoma originating primarily in the lungs is bronchiogenic

2 There is evidence that when the disease is found in the lungs it results from a pathologic (excessive) regeneration following chronic inflammation of the bronchial tree

3 Of the three varieties of cells lining the bronchial mucosa, that is, the ciliated columnar epithelium, the goblet cells and the "basal" cells, only the last are concerned in the process of regeneration of the bronchial mucous membrane It is assumed, therefore, that these cells likewise serve as a sole matrix for primary bronchiogenic tumors

4 Similarly, primary squamous cell epitheliomas and basal cell epitheliomas of the lungs do not result from metaplasia of the pre-existing ciliated columnar epithelium, but originate through protoplasia (indirect metaplasia) of the undifferentiated basal cell of the bronchial mucous membrane

IV CLASSIFICATION

A Microscopic

Apparently not only the inauguration of a neoplasm but its further advance depends on numerous extrinsic and intrinsic factors Thus Ehrlich in transplanting cancer from mouse to rat noticed that the tumor continues to grow in the new host for a few days only, after which time it begins to regress until it finally heals It was further observed that even in a homologous animal a grafted tumor will not always grow in the new host

The mechanism of the animal resistance to a neoplasm is not understood It is possible that a "natural immunity" akin to that observed in infectious diseases, plays likewise a rôle in neoplastic diseases It may be also that the inoculated malignant cells early alter the sensitiveness of the host thus influencing the development of the new growth either by interfering with its further advance, or possibly by "shaping" it Thus in experimental malignant conditions it has been observed that the "virulence" of neoplastic cells undergoes changes under the influence of repeated transplantations, and that a spontaneous cancer in an animal may become arrested and even regress

Since the virtual onset of a visceral cancer in man cannot be estimated the natural history of the disease can rarely be ascertained The classification of inaccessible human cancer and particularly of that originating in the bronchi is, therefore, only tentative, being based on some particular stage of the disease which too often represents the terminal period of the malady

In the preceding chapter evidence has been produced to show that

(1) primary carcinoma of the lungs takes its origin near or at the hilum, (2) that the disease starts in the "basal" cells of the bronchial mucosa Because of this "unitarian" conception the histogenic classification of older observers (from the bronchial mucosa, from the mucous glands, and from the alveolar epithelium) falls to the ground In the following paragraphs the author will therefore consider the

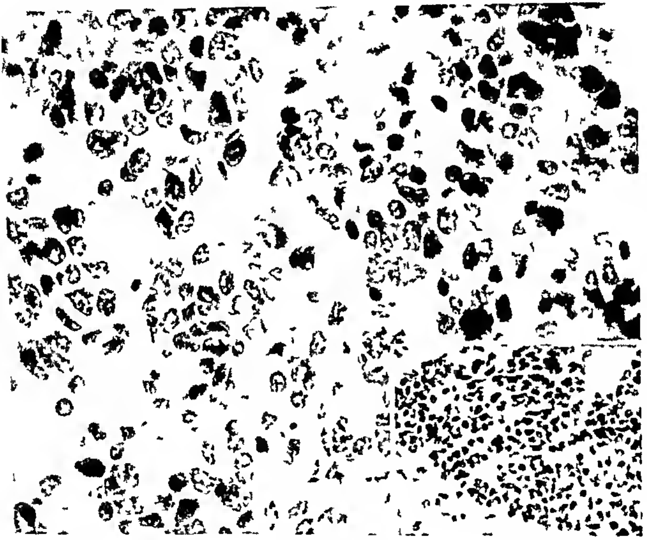

FIG 15 BRONCHIOGENIC MEDULLARY CARCINOMA (SMALL CELLED CANCER)

histologic types of bronchiogenic cancer encountered in the pathologic laboratory

The cellular elements in primary carcinoma of the lungs are exceedingly polymorphic (fig 2, p 399) The morphology of the cells in tumors, as already stated, not only varies, but presents different cellular types in the same specimen and even in the same microscopic field This cellular "colorfulness" is probably connected with the slow advance of the neoplasm or else with some local factors to which pul-

monary cancer is subjected, leading to multiple mutations or to pseudometaplasia (local adaptation) However, the following types may be considered

1 *Bronchiogenic adenocarcinoma* This variety of tumor originating in the bronchi does not vary from tumors of the same type originating in other organs It is made up of either high columnar cells resembling the tall columnar epithelium of the bronchial mucosa without, however, any cilia, or the cells are cuboidal The tubules vary in shape and size having one or many layers of cells There are apparently no differences between the

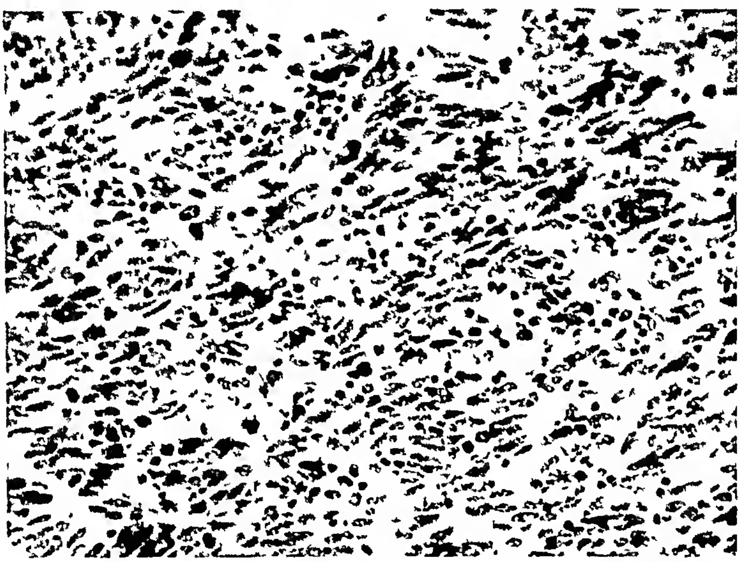

Fig 16 "Oat Cell" Cancer of the Bronchus

two varieties of tumor as far as the malignant qualities are concerned If one is to judge from the clinical course of the illness and also from the occurrence of metastases, the two types possess an equal degree of malignancy However, the columnar-cell adenocarcinoma has probably a more pronounced tendency to invade the pulmonary alveoli (implantation metastases), whereas the cuboidal is probably more apt to invade the blood vessels earlier

2 *Bronchiogenic medullary carcinoma* These tumors are usually made up of small round cells the size of a small lymphocyte (fig 15) There is practically no stroma between single cells or groups of cells This blastoma, too, has a tendency to invade blood vessels, leading virtually to vascular

thromboses It is interesting that the round cell cancer has a peculiar tendency to rapid growth in the liver, whereas the central nervous system shows no metastases The hepatic metastases show a fine stroma, they are well circumscribed, and not infrequently undergo destruction as evidenced by fibrosis In one case studied by the writer the new growth was diagnosed as "sarcoma" of unknown origin, and in another instance the histologic differences between the pulmonary and the hepatic tumors were so

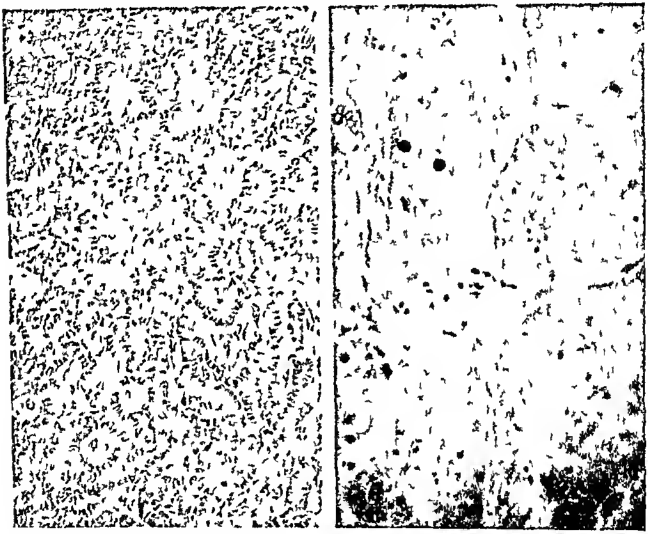

FIG 17 BASAL CELL EPITHELIOMA OF THE LEFT BRONCHUS

pronounced that the diagnosis of a "primary double tumor" was suggestive

3 *"Oat" cell cancers* Barnard has called particular attention to this group of tumors, which were regarded up to recent years as "sarcomas" of the mediastinum (fig 16)

The tumor usually forms a large mass which replaces the lymphatic glands of the posterior and lateral mediastinum and infiltrates the pericardium Histologically the tumor consists essentially of small oval cells with scanty cytoplasm These cells have been likened to oat grains

4 *Bronchiogenic basal cell (nonkeratinizing) epithelioma* (*fig 17*) One patient with this variety of tumor came to the attention of the author The histology of the tumor is as follows The new growth is composed of polyhedral cells having a large cytoplasm and a voluminous vesicular nucleus The cells are arranged in columns and strands from 2 to 3 cells broad which show anastomosis and branching In areas the cells have a tubular arrangement their nuclei are compressed, pushed toward the

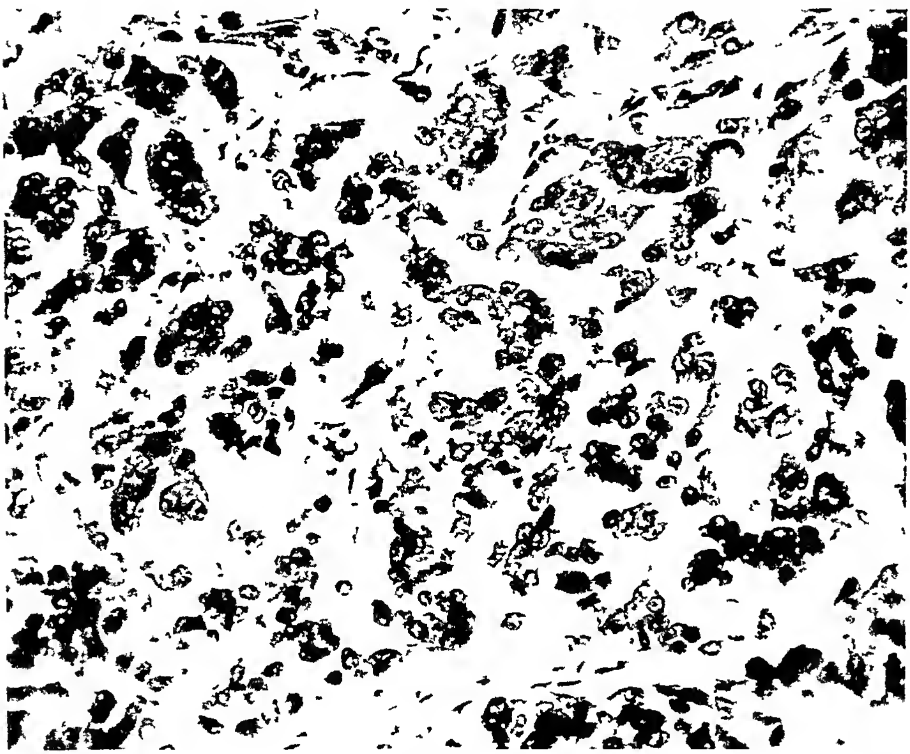

Fig 18 Basal Cell Epithelioma of Bronchus
The multinucleated giant cells must be noticed

periphery, the whole structure having a rosette-like appearance In places the tumor is rather solid, being arranged in small clumps of cells or rows of cells Multinucleated cells are found to occupy wide areas (fig 18)

The cells contain a variety of inclusions resembling the "parasites" described by some writers, and occasionally "bird's eye" inclusions Round globules of a different size, stained black with methylen-blue-eosin are seen here and there There is no keratinization or "pearl" formation Much fat is seen in the cells as well as between them

The stroma of the tumor consists of a loose, edematous connective tissue infiltrated with small round cells The tumor is sharply demarcated from the pulmonary parenchyma, which shows compression of the alveoli and thickening of the alveolar wall Mitotic figures are rarely seen

The lymph nodes show no invasion by tumor, and no metastases are found in the other lung or in other visceral organs

5 *Bronchogenic squamous cell (keratinizing) epithelioma (fig 19)* This variety of tumor shows a great polymorphism

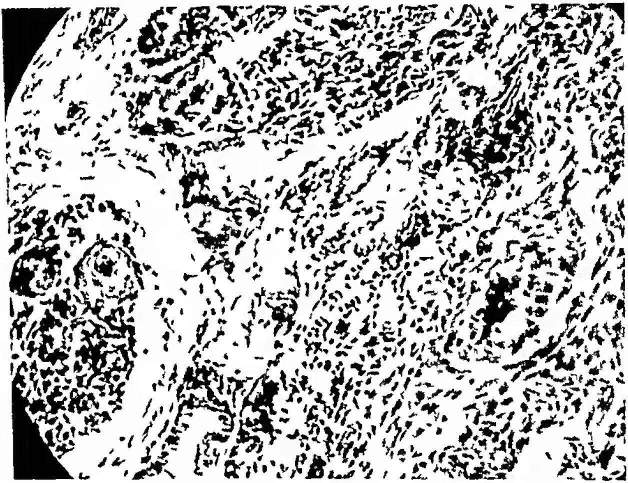

Fig 19 Epidermoid Carcinoma of Right Bronchus
The formation of "pearls" must be noticed

The tumor grows without any definite arrangement Nests or masses of cells are seen scattered over the sections surrounded by thick bands of dense fibrous tissue Individual tumor cells are large, polygonal or elongated and irregular The vesicular nucleus occupies the greater part of the cell it is large, rich in chromatin containing a centrally located, deeply-stained nucleolus Large cells with many nuclei resembling giant cells are encountered here and there Masses of cells with the typical appearance of the cornified epithelium found in the so called "pearls" of the epidermoid carcinoma are seen now and then

The pleura is as a rule involved by tumor Metastases to the other lung and to distant organs are common

Comment

A histologic classification of malignant tumors is of importance as a point of departure for the treatment and the prognosis of the disease An attempt to "grade" some visceral cancers on a histologic basis according to their malignant qualities was undertaken by Broders of the Mayo Clinic with interesting results A contribution along these lines was made by Cushing and Bailey with regard to cerebral tumors In a study of gliomas extending over a period of two decades Cushing posed the questions 1 What is the basis of the structural variability shown by these gliomatous tumors? 2 Has their histological variation any clinical significance? Similar studies on a large scale have never been made on visceral cancers, and particularly on those which originate in the bronchi The bronchiogenic cancer, as referred to in this study, was a *terra incognita* to the surgeon, clinician and pathologist alike Even the roentgenologist rarely committed himself in making a diagnosis of this disease With the extensive use of new methods of investigation (surgery, bronchoscopy, injections of iodized oil, roentgen-rays) a future opportunity which may be of practical importance will be presented for tracing the virtual course of the disease and then reconstructing the several stages of these blastomas

From the author's study of the histologic types it followed that one variety of tumor, namely, the basal cell cancer, is of particular interest, representing apparently an entity closely related to that found in the skin The tumor does not metastasize even to the tributary lymph nodes, and has no tendency to degenerate A patient with this type of cancer was under observation sixteen months and, what is interesting, the size of the new growth controlled by several roentgen-ray examinations has remained practically unchanged during this period The duration of the disease in this case, as in all the other cases studied, could not be ascertained However, the condition lasted apparently many years The incidence of the tumor cannot be estimated since previous observers described it as a sarcoma of the lung, and in many instances histologic reports are entirely lacking This type of new growth is of interest in connection with radiation and roentgen-ray treatments of malignant tumors

B Macroscopic

Weller from "a survey in the light of the hundred reports of cases now available" discriminated three types of tumors (1) a type associated with the hilum, (2) a nodular type, and (3) a diffuse type

FIG 20 BASAL CELL EPITHELIOMA OF THE LEFT BRONCHUS

That this classification, which is also that of most writers, is fallacious will be demonstrated in the examples following

Example 1 (fig 20) Basal cell epithelioma of left bronchus without metastases

The tumor was grayish white, moderately firm and friable It was composed of one large mass occupying the entire apical part of the left lung The rest of the lung with the exception of the lower segments of the lower lobe, appeared as if it were split vertically in two equal parts the anterior—emphysematous and free of tumor, the posterior representing a solid

FIG 21 EPIDERMOID CARCINOMA OF RIGHT BRONCHUS

neoplastic block The new growth originated apparently in a small bronchiole It was well demarcated from the surrounding pulmonary tissue and it did not metastasize

The patient in this case died of emaciation with deep cachexia The tumor is an example of the "massif type"

Example 2 (fig 21) Epidermoid carcinoma of the right bronchus with widespread metastases including the myocardium

The pleura over the posterior border of the right lung ranged from 3 to 6 mm in thickness, and consisted of white, fibrous tissue with firmer white plaques, from 2 to 4 mm thick, composed of friable tumor material There were a few pigmented lymph nodes at the anterior border of the diaphragm which contained numerous white nodules

The left primary bronchus was normal The right was practically occluded 2 cm below the bifurcation Anteriorly, the wall of the right primary bronchus was replaced by a friable, white tumor tissue which on pressure exuded soft, white material which on subsequent examination proved to contain desquamated epithelial cells, the largest part keratinized The only branch of the right primary bronchus that could be found was one leading to the upper part of the right lobe, and the orifice of this bronchus was almost completely friable tumor, about 3 cm in thickness, which extended downward along the inner posterior margin of the lung for a distance of 8 cm Anteriorly, the tumor which had replaced the wall of the primary bronchus extended by direct continuity over the anterior surface of the aorta forming a layer 1 cm thick which extended upward over the ascending portion of the arch

Two parallel incisions were made through the posterior borders of the lungs and showed that all the lung was atelectatic, with here and there small bronchiectatic cavities All of the upper lobe was tough and fibrous, and in the peripheral portion of the lung were a few nodules, a few centimeters in diameter, of friable tissue These tumor nodules were most abundant in the lower lobe

The left lung contained no tumor On the inner surface of the lower lobe, that is in contact with the pericardium, there were two plaques of tumor each a few millimeters thick and 1 cm in width

The tumor in this patient originated in the right bronchus, a little below the bifurcation, leading to a marked thickening of the bronchial wall, spreading along and encircling the bronchi and blood vessels It also formed a tumor mass within the thoracic cavity

Some authors recognize an infiltrating type of pulmonary cancer, which indeed is a trait proper to malignant tumors in general Others describe a pleural type of bronchiogenic carcinoma However, a marked involvement of the pleura occurred early in most cases studied by the writer which cannot, therefore, be considered as a discriminating feature

As seen, this tumor although advanced does not correspond to any of the types given by older observers in their classification

Example 3 (fig 22) Bronchiogenic carcinoma of the right lung with metastases to regional lymph nodes and left kidney

FIG 22 BRONCHIOGENIC CARCINOMA WITH CAVITY FORMATION
Massive or Lobar type

Lungs The right lung could be divided into two parts by the much thickened interlobar septum The upper part was atelectatic showing thickened bronchi, but no tumor The lower part was replaced by a large tumor measuring in its larger diameter 12 cm On cut surface it was resilient grayish white and somewhat granular The central part of the new growth was dirty red and soft, being made up of clotted blood When

this clot was removed the neoplasm appeared as a hollow mass which occupied the middle and lower lobes The wall of the cavity was dirty gray and irregular, forming mammilary projections The lower branch of the right bronchus opened into the cavity A few blood vessels also protruded above the surface of tumor having their lumen open

The tumor apparently started in a small branch of the middle or the lower lobe

Fig 23 The "Infiltrating" Type of Bronchiogenic Cancer

Here is another example of an advanced tumor which may be regarded as the massif or lobar type The "central necrosis" with the cavity formation is an interesting feature of many bronchiogenic cancers This is of particular interest to the clinician because the clinical picture in such cases is that of pulmonary abscess, which will be discussed shortly

Example 4 (fig 23) Bronchiogenic cancer of right lung, metastatic to left lung, pleura, bones, and liver

Lungs The left lung weighed 1100 grams The organ had a normal color and was enlarged, covering the heart On palpation, it had a finely-granular feel as if it were filled with very small glass beads Between the nodules, the lung was normal, being elastic and crepitant On section, the cut surface appeared to be peppered with disseminated, grayish nodules, from 2 to 3 mm in diameter, which gave the lung a coaresly-granular feel The mucosa of the bronchi was congested, but did not show any evidence of invasion by tumor The vessels were not remarkable on gross examination

The right lung (fig 23) weighed 600 grams The organ was contracted and occupied only the upper part of the pleural cavity On palpation, the lung was firm and had a somewhat beefy feel The surface of the lung was smooth and glistening At the apex, the pleura, which was here about 0 5 cm in thickness, was firmly adherent to the lung, and the lung *in toto* looked as if it were suspended by its apex in the pleural cavity On section, the lung somewhat resembled a pneumonic lung in the stage of red hepatization In some smaller vessels, grayish, pin-point elevations were conspicuous and seemed to be tumor nodules The bronchial lymph nodes were enlarged and firm

The tumor in this case was remarkable in that it infiltrated both lungs which is not common The left lung showed a typical nodular structure and the right (fig 23) represented a mass of peculiar, beefy tissue Here the tumor diffusely invaded the alveoli lining their walls and forming papillary projections in the air sacs It also metastasized to the pleura (leading to its very marked thickening), to the liver and to the bones The neoplasm which apparently originated in a small bronchiole in the right lung was of the massif type being at the same time infiltrating, nodular and pleural

Example 5 (fig 24) Bronchiogenic carcinoma of left lung, metastatic to pleura, lymph nodes, right lung, adrenals, bones, skull, liver, cerebrum and cerebellum Also bronchiectatic abscesses and hydrothorax

Lungs The entire left upper lobe was extensively infiltrated with grayish-white tumor, the center of which was necrotic The lower lobe of the same lung contained scattered tumor nodules, the largest being 1 cm in diameter The pleura overlying the lung was thickened and firmly adherent both to the pericardium and to the lung

The right lung contained several firm metastatic nodules, the largest of which measured 2 cm in diameter Tumor also infiltrated the bronchial lymph nodes

FIG 24 THE "NODULAR MASSIVE" TYPE OF BRONCHIAL CANCER

On cut surface the main neoplasm was made up of numerous round nodular masses which have fused together forming one massif tumor block involving the entire left upper and middle lobes (fig 24)

The bronchus leading to the left upper lobe was obliterated The bronchi and bronchioles to the lower lobe showed bronchiectatic cavities and abscesses The blood vessels showed their lumen infiltrated by the new growth Tumor also was found in the mesenteric, retroperitoneal and cervical lymph nodes There were metastases in the ribs, skull, liver, cerebrum and cerebellum

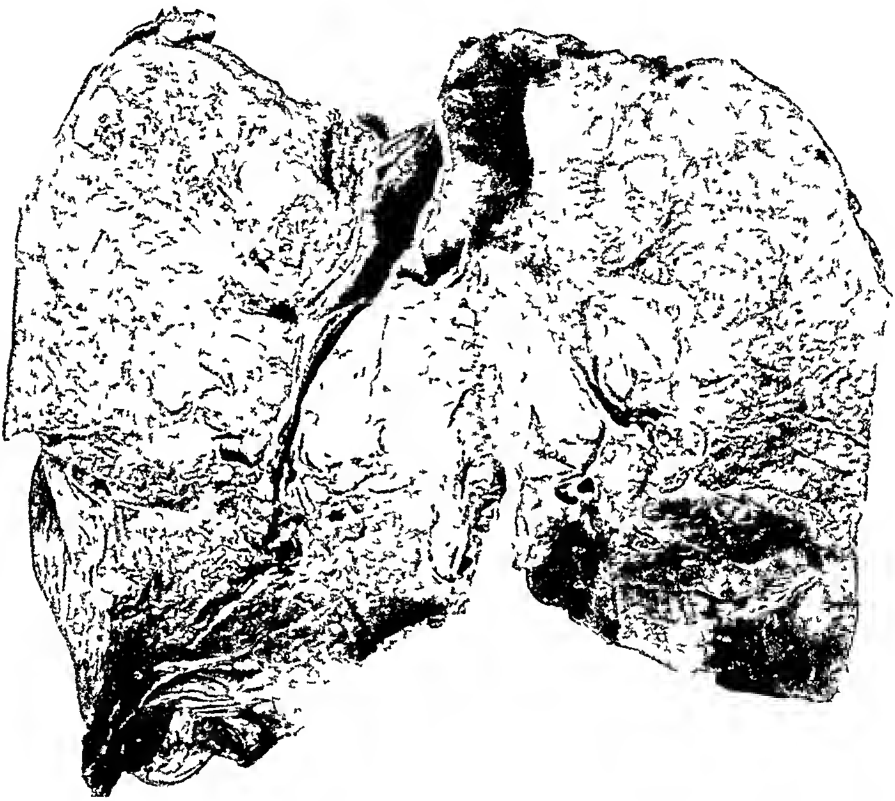

FIG 25 ANOTHER EXAMPLE OF THE "NODULAR-MASSIVE" TYPE OF A CANCER OF THE BRONCHUS

In this patient, too, the tumor at necropsy was in an advanced stage Originally it probably was of the nodular variety, but as time went on the nodules coalesced, forming a massive growth involving the entire upper and middle lobes and also metastasizing to the other lung The neoplasm which started in the vicinity of the hilum represented then a massive block made up of fused nodules

Example 6 (fig 25) Right bronchiogenic cancer, metastatic to hilum, lymph nodes, pleura, adrenals and left kidney

The pleural cavities The right pleural cavity contained 1200 cc of a straw colored fluid

The lungs The right lung weighed 2015 grams It was voluminous, heavy and firm On cut surface the main bronchus was much narrowed by the solid tumor and its upper and middle divisions were obliterated The main tumor was apparently confined to the mediastinum lying underneath the bifurcation of the trachea, between the two main bronchi, accompanying the left bronchus for only a short distance The right bronchus, however, was followed by tumor on its mediastinal aspect throughout its entire length up to the entrance into the lower lobe The rest of the lung represented a mosaic appearance being composed of nodules of various size and color Some of the nodules had a typical cheesy aspect like that seen in tuberculosis, others were deeply tinged with a yellowish substance, and still others had an admixture of carbon pigment The lymph nodes were involved throughout the lungs and also along the trachea The pleura was thick, leathery and also was heavily invaded by tumor

Metastases were found in the adrenals, left kidney and brain A tumor thrombus occluded the superior vena cava for 2 cm beginning at the auricular end The thrombus was firmly attached to the wall of the vein Tumor invading the vein was found also above this large thrombus There was a myocarditis, atherosclerosis and diverticulosis of the colon

This advanced neoplasm involved the entire lung, composed of innumerable nodular masses forming one solid block In the early stages this tumor, like that in the preceding case, represented what is designated as the nodular type Here, then, is a combination of the massive, pleural, and the nodular varieties of a bronchiogenic cancer

Example 7 (fig 26) Bronchiogenic adenocarcinoma of right upper and middle pulmonary lobes, metastases to brain, liver, adrenals and kidney

Lungs The right lung was considerably larger than the left The right main bronchus showed no disease Beginning with the first smaller division the bronchial lumen was narrowed and its wall thickened The middle and lower bronchial branches were patent The branch to the upper lobe was patent for about 1 5 cm , the remainder being obliterated

The tumor involved the base of the upper lobe and the apices of the middle and the lower lobes, leading to a symphysis of the three lobes The left lung showed no tumor

The bronchiogenic tumor involved an insignificant part of the lung, the death of the patient being precipitated by multiple cerebral metastases The new growth could be regarded as being rather in an "early" stage of its development It started in a small bronchus at

Fig 26 An "Early" Cancer of Bronchus, Unclassifiable

some distance from the hilum and grew as a solid mass, spreading toward all three lobes It is impossible to ascertain whether such a tumor (had the patient lived long enough) would ultimately take a massive, a nodular or some other aspect

Example 8 (fig 27) Bronchiogenic cancer of left lung, metastases to regional lymph nodes, liver, kidneys, adrenals and bones

The lungs The left lung showed a tumor mass which originated near the hilum extending toward the periphery It spread along the bronchi and

Fig 27 The "Hilum" Type of Cancer of the Bronchus

the blood vessels, circling them and leading to narrowing and occlusion of the lumen The tumor was gray and firm and at the periphery showed papillary projections like those seen in cancer of the breast

The patient in this case died of an extensive bronchopneumonia at a period when the pulmonary new growth had not advanced

As can be seen this case is representative of the hilum type Had the patient lived longer, the tumor which grew as a solid mass would have probably taken a "massif" aspect

Example 9 (fig 28) Bronchiogenic cancer of the upper lobe of the left lung, with multiple metastases to brain, pancreas and right kidney

Fig 28 An "Early" Bronchiogenic Cancer, Unclassifiable, Tr Trachea

Lungs The upper lobe of the left lung was adherent to the thoracic wall posteriorly and partly laterally

In the left bronchus, at the level of its first division there was roughening of the bronchial mucosa and a few grayish-white nodules This was conspicuous throughout the entire length of the first bronchial branch distributed to the upper lobe The bronchial wall was markedly thickened and its lumen was largely obliterated

The tumor invaded the left hilum lymph nodes, which were greatly enlarged. A voluminous node measuring 3 by 5 cm was found in front of the trachea at the level of the bifurcation, lying close to the pulmonary vein. Another mass measuring about 5 cm in diameter was found lying underneath the arch of the aorta surrounding it for about one third of its diameter, and lying "astride" on the left bronchus. A few nodules measuring about 3 mm in diameter were found in the upper lobe which also showed ateleclasis and infarction. The tumor metastasized to the pancreas, to the kidney, and to the brain.

It is remarkable that in the presence of the apparently early bronchial growth the neoplasm in this patient heavily infiltrated the regional lymph nodes, metastasized to distant parts of the same lung and to other structures. The pulmonary tumor could not be classified according to its macroscopic appearance.

Example 10 (figs 29 and 30). Right bronchiogenic cancer with metastases to lymph nodes, left lung, liver, kidney, adrenal and brain.

Lung. The right bronchus and the eparterial branch distributed to the upper lobe was normal. Of the two divisions of the hyparterial branch, the lower, which enters the lower lobe and its ramifications, were patent throughout and showed no disease. The branch for the middle lobe was patent for about 5 mm and the mucosa here was smooth and normal. Below that, the bronchial lumen was virtually occluded although a very fine probe could pass for about 1.5 cm.

When the lobe and the bronchus were cut the following picture was seen: the upper wall of the middle bronchus beginning at its separation from the main bronchus was destroyed, being "amalgamated" with a well circumscribed tumor mass. The white friable new growth measured about 2 cm in diameter being surrounded above by the pulmonary vessels and below by the middle lobe bronchial branch from which it was inseparable. On further inspection one could notice that only a trifle of the median lobe at its base remained free from disease while the rest was replaced by a new growth which measured about 12 cm in diameter. This was composed of two parts having different aspects: one, gray and firm, was confined to the upper circumference of the lobe, the other, soft and necrotic looked like a capillary hemangioma. The parts of the lung free from tumor showed bronchopneumonia and emphysema.

The left lung showed no pathologic changes. The main artery of the left lower lobe showed a thrombus, small thrombi were found also in smaller

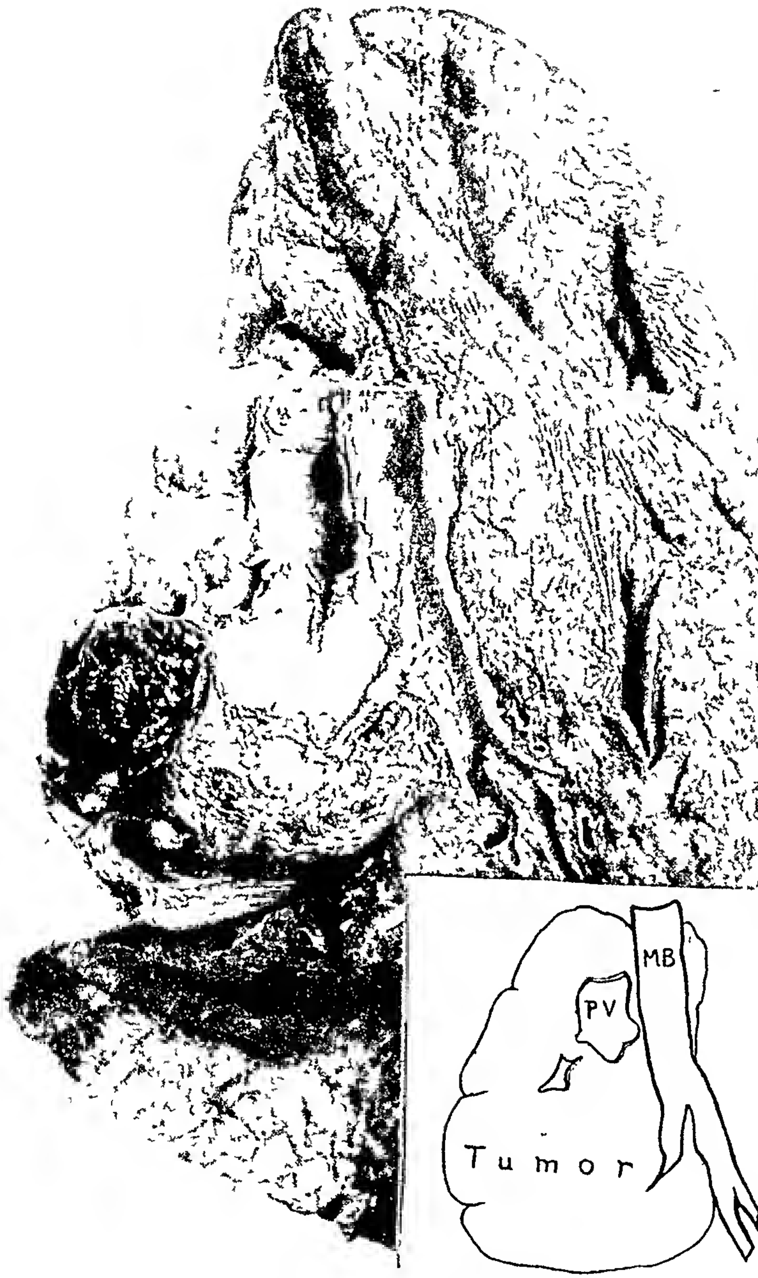

FIG 29 THE "LOBAR-HILUM" TYPE OF BRONCHIAL CANCER
Dorsal aspect, *M B*, Main bronchus, *P V*, Pulmonary vein

FIG 30 THE FRONTAL ASPECT OF THE CANCER SHOWN IN FIGURE 29

vessels A small tumor nodule was found in the upper lobe of the lung Metastases were present in the brain, in the liver, in the lower pole of the right kidney and also in the right adrenal

The right carotid artery was thrombosed with marked atheroma proximal to the site of the thrombus A small ulcerated area with a small thrombus attached was found beside the right coronary artery

The tumor in this case, as in all cases studied, originated in the mucosa of the bronchus in the vicinity of the hilum It grew toward the bronchial lumen (endobronchial) and toward the pulmonary parenchyma The neoplasm represented a ball-like mass occupying the entire middle lobe involving at the boundary the adjacent lobes

This "Lobar-hilum" cancer showed a tendency to infiltrate the healthy tissue in a diffuse way, it was also markedly necrotic

General considerations

The macroscopic classification of tumors may be either regional being based on the localization of the growth (for example, cancer of the pylorus, of the fundus, or of the cardia of the stomach) or it may be based on their gross appearance (fungating type, ulcerating type, and so on) The classification of bronchiogenic cancers as "synthesized" by Weller from "hundreds of reports of cases" (which indeed is the classification of most pathologists) is inconsistent because it is based on one hand on the topography, that is on the region where the blastoma started (hilum), on the other hand on the macroscopic appearance of the neoplasms (nodular, diffuse)

Topographically primary carcinoma of the lungs, as said above, originates near or around the hilum In rare instances has a case been observed where a bronchiogenic cancer was situated somewhere in the pulmonary parenchyma without being in direct connection with the pulmonary root Apparently the hilum, or an area close to it, is the site *par excellence* where cancer of the bronchus takes its origin

The distinction of a diffuse and a nodular type is not altogether satisfactory since, as shown in the cited examples, a tumor made up at one time of nodules may be transformed at a later period into a diffuse variety and vice versa The picture, in brief, is not uniform, depending upon the duration of the disease, the intercurrent events and upon factors which cannot be ascertained

The tumors in the series studied by the writer could be divided into the far advanced and into the early, or those that have involved the pulmonary parenchyma for a short distance only

The advanced tumors represented in most instances a solid block of tissue with or without necrosis, made up either of one diffuse mass or of fused nodular masses In instances the massive growth was excavated in the center forming large central "abscesses" In one case, the bronchogenic cancer occupied the entire middle pulmonary lobe, and at first glance it appeared that the tumor could be "amputated" The cancer, however, which was necrotic resembling a large degenerated hemangioma, contained actively growing neoplastic tissue at the periphery, where it came in contact with the pulmonary parenchyma "contaminating" it and leading to adhesions between the lobes

In all of these tumors, with the exception of three, there was involvement of the tracheobronchial lymph nodes, and also metastases to distant organs

The pleura was diffusely infiltrated by neoplastic cells in most cases, its thickness varying from 2 to 5 mm There always was an adhesive pleuritis In many instances there was a hydrothorax either bilateral or confined to the side where the tumor started In two cases there was a hemothorax In a few cases the tumor invaded the lumen of the large blood vessels, forming macroscopic thrombi In one instance the new growth compressed the vessels, leading to stasis and to peripheral edema

In the "early" cases the primary cancer was located near the hilum originating in a primary bronchus or in one of its early divisions In the area where the tumor started, the bronchial wall was thickened as a result of infiltration by neoplastic cells The malignant new growth usually spread in both directions (1) toward the lumen where it formed either mammillary projections or a solid mass, resulting in a narrowing of the bronchial lumen, (2) toward the pulmonary parenchyma replacing it either diffusely or by fine projections

At the border of the new growth the blood vessels often showed thickening of their wall which under the microscope appeared to be due to either degenerated vascular changes or to invasion by malignant cells

The carcinoma presented a translucent surface often studded with pigment and opaque, seminecrotic tissue In many sections through these tumors there were seen small and large blood vessels occluded by recent or organized thrombi and in one instance the tumor extended into a large vessel adjacent to the primary bronchus involved Occasionally, small infarcts of the lungs were seen, small nodular metastases to the same lung were noticed at the "early" stage in a few instances There were, as a rule, some pathologic changes in the same lobe of the lung, which was the site of the tumor for example, compensatory emphysema, infarction and recent inflammatory processes

In studying reports of cases from medical literature one is impressed by the multiplicity of classifications of pulmonary cancer as given by different observers This is due to the fact that different stages of the disease were investigated, and also as stated, to the actual protean aspect of bronchiogenic cancer

Unlike cancers of other viscera which often lead to a premature "mechanical" death (stricture of the esophagus, obstruction of the bowel, or of the stomach), a bronchiogenic malignant disease goes on unnoticed possibly for years causing only mild bronchopulmonary symptoms imitating inflammatory diseases of the lung During its protracted course it may then take different aspects depending upon such factors as metastasis to the same lung, secondary infection with suppuration of the lung, erosion of blood vessels in and around the tumor causing hemorrhage and disintegration of the new growth, pulmonary atelectasis or pneumothorax, *pleuritis carcinomatosa* and pleurisy

In brief then the gross classification of the tumor as given by pathologists is as unsatisfactory as the microscopic discrimination Here, too, further studies of the natural history of the blastoma will probably furnish a comprehensive classification which will be of a practical importance and of a theoretical interest

V METASTASES

The problem of metastases provoked a deep interest of the older pathologist An attempt to investigate the question experimentally was first made by Cohnheim who followed the fate of intravenously injected particles of embryonic periost He observed that in the lungs

the injected material was at first transformed into bone but was ultimately destroyed From this observation Cohnheim drew the conclusion that the formation of a secondary growth results not merely from the lodgment of cells somewhere in the body but depends also upon the host himself, that is upon the absorbing properties of the organism

Lubarsch (1895 and 1906) expressed the belief that two factors are required for the formation of metastasis the loss of the "absorbing" power by the organism, the toxicity of the malignant cells According to this author malignant cells reach the regional lymph nodes and the blood stream in "waves," the first of which are destroyed, thus liberating a "toxin" which neutralizes the natural force of the organism to resist and to destroy malignant cells Borst distinguished a "premetastatic period" when malignant cells invade the circulation and settle in tissues without causing a secondary growth, and a "metastastic period" when there occurs a proliferation of secondary tumors Finally Ehrlich interpreted the phenomenon of metastasis on an immunobiologic basis, namely, on the "athreptic theory" devised by him

Ehrlich observed that a cancer transplanted from a mouse to a rat continues to grow in the new host for about seven days after which time it begins to regress until it finally heals, but the same tumor retransplanted in the early stages of its regression to a healthy mouse regains its former proliferative activity (The experiments are known as "Gross Experiments" or "Zick-Zack Versuche") The failure of the tumor to thrive in the new host was explained by Ehrlich as being due to the lack in the organism of proper (specific) foodstuffs Ehrlich also explained in the light of the athreptic theory the fact observed by him, that slowly growing tumors and tumors of smaller size give more abundant metastases than rapidly growing and large tumors

Kitain from the service of Lubarsch produced evidence to show that in human cancer widespread metastases were much more commonly seen in the slowly advancing tumors

However Pearce and Brown in a study of the occurrence and distribution of metastases of a malignant tumor in a group of 191 rabbits noted that "no constant relationship existed between the rate of

growth or the size attained by the primary tumor and the occurrence of metastases in distant organs" They have observed that pulmonary metastases occurred early and ahead of the general involvement of other organs The secondary tumors in the lungs underwent, however, spontaneous resolution without leaving any gross evidence of their previous existence The hepatic metastases were much larger and more numerous than the pulmonary because the opportunities for growth in the liver are, according to these authors better than in the lungs The fact that the liver was less often involved by secondary tumors than the lungs is merely due to the fact that it is less accessible to tumor cells

It is interesting that the frequency of metastases diminishes with the distance from the central axis of the body This phenomenon, too, is not entirely due to the nature of the tissues composing these parts, since metastases are comparatively frequent in tissues of the same order but nearer the body axis Like Cohnheim and Ehrlich, Pearce and Brown lay stress upon the host as the "prime factor in determining the course of the disease"

Primary carcinoma of the lungs possesses a vigorous metastatic power, and its metastases are, as a rule, widespread Thus Adler found that of 374 cases of this disease, 280 showed secondary tumors In order of frequency, the regional lymph nodes, liver, pleura and lungs were found to occupy the first place, while the brain and bones were said to be much less frequently involved Kikuth in a series of 240 cases found the following distribution of metastases liver, 70, bones, 48, lungs, 43, brain, 31, kidney, 25, suprarenals, 21, Pancreas, 11, thyroid, 5, cardiac muscle, 4, intestines, 3, stomach, 2, spleen, 2, gallbladder, 1, and ovary, 1 Reports by more recent writers are to the effect that a non metastasizing bronchiogenic cancer is a rare finding

In the series of 47 cases studied by the author all but 3 tumors showed multiple metastases One of the nonmetastasizing cancers was a basal cell epithelioma closely resembling the same variety of tumor found in the skin Those tumors that have metastasized invaded primarily the tributary lymph nodes, then the lungs, the pleura, the liver, the brain and the suprarenals The bones, too, were apparently frequently involved, judging from the clinical and roent-

genological appearances Histologic examination of the skeleton was, however, rarely performed, and in one instance, at the postmortem examination, the long bones were infiltrated with cancer cells without any previous clinical manifestations and without any outward changes It is possible then that a systematic investigation of bones for secondary tumors would furnish much higher figures than recorded

The frequent occurrence of metastases in bronchiogenic cancer was attributed to the supposed high malignant character of the tumor, and also to the fact that the lungs are abundantly supplied with blood and lymph vessels, that is, with a rich net of channels facilitating the transport of tumor cells It is probable however, that in man as in the lower animals, the occurrence and distribution of the secondary tumors "represents an expression of the interaction between tumor and host" The observation made by Pearce and Brown that in their experiments the frequency of metastases diminished with the distance from the central axis of the body holds apparently true also for bronchiogenic cancers In only very rare instances were metastases found in the abdominal viscera below the region of the kidneys, while the liver and the brain were probably the commonest seats for secondary tumors in this disease

The incidence of metastases to bones from primary carcinoma of the lung cannot be ascertained because of the fact that the skeleton, as referred to, was rarely investigated Likewise the occurrence of intracranial secondary tumors cannot be stated with accuracy for the available statistics often fail to state whether the brains of all the included cases were examined Thus Dosquet investigated the necropsy material from the institutes of pathology at Kiel and Berlin, respectively, and found metastases to the central nervous system in 33 of 105 cases of bronchiogenic carcinomas Seyfarth found involvement of the brain in 30 of 309 necropsies on patients with pulmonary cancer and Simpson observed intracranial metastases in 19 of 139 postmortem examinations on patients with this condition Neither of these authors stated whether the brain was examined in all of the necropsies of their series

Forty-seven cases of bronchiogenic cancer have been observed by the present writer and in sixteen of these metastases to the central nervous system were verified either at operation or at necropsy or

by both procedures (In one patient the diagnosis was based on the clinical findings only) In the remainder there was either no anatomical evidence of the presence of metastases to the brain or the central nervous system was not examined Thirteen of the sixteen cases were unusual in that they were diagnosed as "tumor of the brain suspect "

The manner in which carcinoma of the lungs reaches the bones and the central nervous system is of interest because of its frequent occurrence, and because cancer as commonly accepted spreads by way of lymphatics, which are lacking in these organs

That the bone marrow possesses no lymphatics was for the first time noted by V Recklinghausen Piney, in a recent investigation injected the periosteal lymphatics and observed that the injected material passed from these structures through the bone and into the endosteal channels, he could not, however, force the mass from these channels into the bone marrow

It was shown that within the red bone marrow the blood vessels break up into many wide and tortuous thin walled channels thus causing a marked slowing of the blood stream Tumor cells then which have gained entrance to the blood stream "settle" in the sluggish circulation which is in the center of the bones within the marrow cavities, whence they reach the periphery

The central nervous system was believed once to be provided with a double set of lymph vessels, (1) the lymph spaces of Virchow-Robin which were claimed to lie between the vascular adventitia and the *intima piae,* (2) the lymphatic spaces of His, which were believed to be between the *intima piae* and the *limitans gliae*

Subsequent investigations have shown convincingly that the lymphatics noted by His are artifacts due to injections of the heavy metal Moreover, the lymph spaces of Virchow-Robin are very likely artificial formations and owe their existence, analogous to those of His, to injections of material from outside or probably due to pathologic factors

More recently Held affirmed that spaces in the central nervous system "acting as lymphatics" are present not outside but within the vessel wall, that is, between the media and the adventitia of the blood vessels, while Spielmeyer was of the opinon that the entire vascular coat is made up of "lymphatic spaces " The adventitia of the cerebral vessels when treated with silver tannin discloses, according to this author, a fine reticular structure composed of intercommunicating compartments which are particularly

conspicuous in conditions such as sleeping sickness The German workers have designated these so called lymphatics as "adventitial spaces" of Virchow-Robin (Virchow Robinsche adventitielle Lymphräume)

Apparently the lymphatics of Held and Spielmeyer like those of Virchow and Robin are no more than artifacts In the cerebral vessels as in the visceral one notices the customary fenestration (membrana fenestrata) and

FIG 31 GREATLY DILATED VASA VASORUM IN A CASE OF A GLIOMA OF THE BRAIN

also the vasa vasorum In some pathologic processes the latter increase in number and dilate, forming spaces of various size which are erroneously interpreted as lymph channels (fig 31)

The "body fluid" of the central nervous system is the cerebrospinal fluid, extracted from the blood and filtered or possibly secreted by the choroid plexus (called by some investigators "choroid plexus gland") From the latter through the foramen of Munro, third ventricle aqueduct of Sylvius and fourth ventricle and thence via the foramina it reaches the subarachnoid spaces It is believed that the cerebrospinal fluid is absorbed

by way of the arachnoid villi into the great sagittal sinus, and by way of the perineural spaces, the latter being defined as an accessory drainage The perineural spaces convey the fluid to the tissue spaces and through the agency of the latter intervening it is taken up by the cervical lymphatics (Weed)

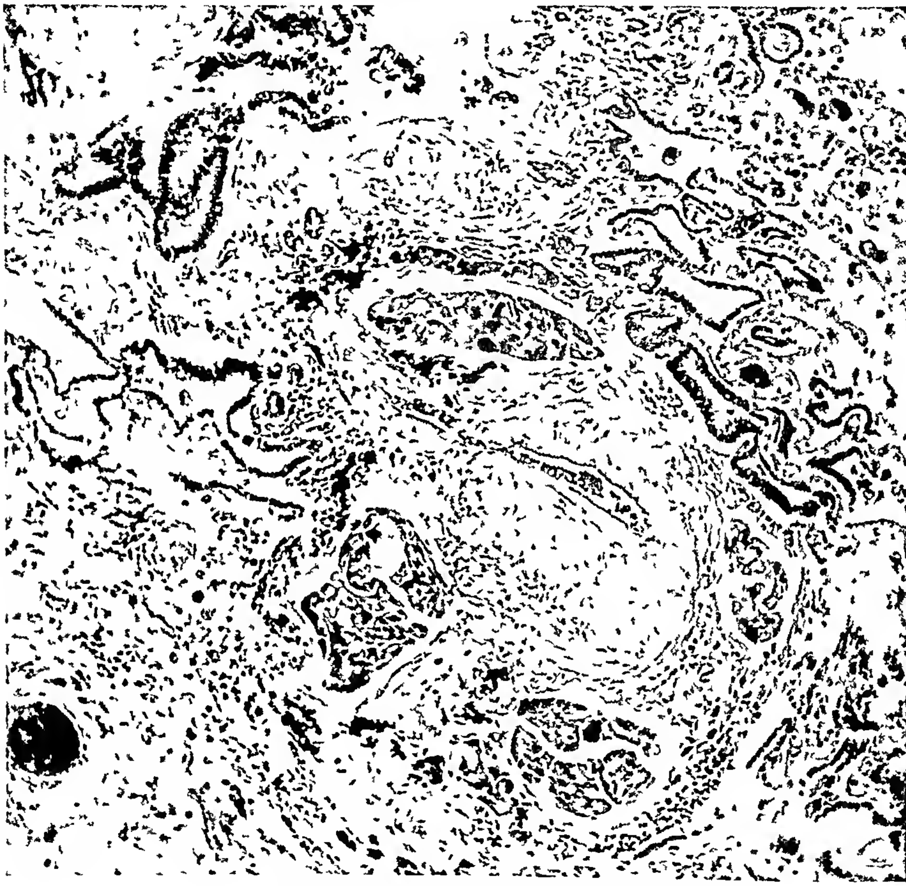

Fig 32 Propagation of Cancer Via the Perivascular Lymphatics, Which are Distended and Filled with Tumor

The vessel shows an endoarteritis obliterans The glandular structures seen outside the vessel are pulmonary alveoli that have been invaded by columnar and culoidal cells from the bronchioles This is discussed in section III entitled Histogenesis

In a study of a metastatic cerebral carcinoma from the breast, Hassin believed that the tumor reached the meninges *via* the perineural spaces in the following manner from the periphery the new growth reached the lymphatics of the neck whence, *via* the tissue spaces to

perineural spaces, "climbing" upstream to the meninges, it finally reached the brain A few other writers described the same pathway for intracranial metastases from a bronchiogenic cancer

At the present time there is a general agreement that cancer metastasizes to distant organs by way of every possible channel Letulle and Jacquelin produced evidence to show that the transmission of

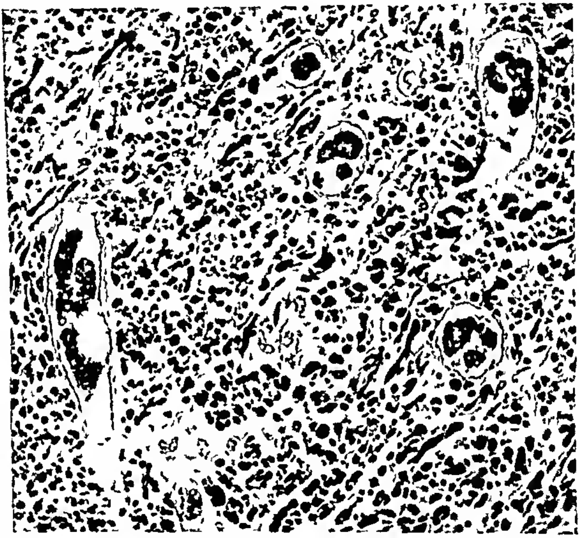

FIG 33 SHOWING TUMOR CELLS IN THE CIRCULATION IN A SECTION FROM THE HEART
A case of a bronchiogenic carcinoma

tumor from one lung to the other was effected by way of the bronchi, namely, by implantation ("metastase aerienne") Goldmann affirmed that mammary cancer is often propagated by way of the lactiferous ducts The transmission of a carcinoma *via* the lymphatics (Fig 32), held by the older pathologists as being the essential pathway for the spread of an epithelial malignant disease, was stressed in recent years by Handley, who produced evidence to show that it is effected in two

the essential one Goldmann has shown that in experimental cancer the blood vessels undergo early pathologic changes This is particularly marked in the veins, which show degenerative changes at the beginning of the disease, while the arteries resist damage for a longer time, and, as in inflammatory conditions of bacterial or toxic origin, they play probably for some time the rôle of "insulators"

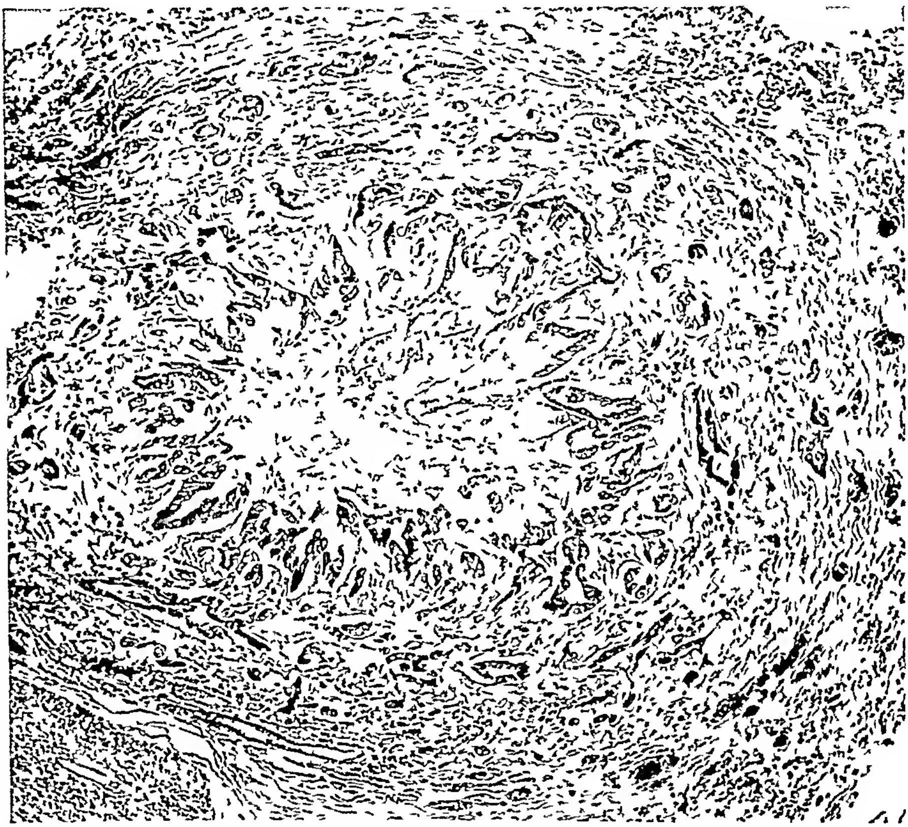

FIG 36 SHOWING INVASION OF THE VASCULAR COAT AND THE VASA VASORUM BY BRONCHIOGENIC ADENOCARCINOMA

Tumor cells are likewise found along the intima of the vessel There is an early stage of an obliterating endoarteritis

Neoplastic cells aggressibly invade the vascular coat, being disseminated throughout the vessel wall by way of the vasa vasorum (figs 35 and 36), this is suggested by the fact that in the arteries, where nutrient vessels are particularly prominent in the outer coats, the

tumor is essentially "periarterial," while in the thin walled veins the new growth is seen as an endophlebitis

Hematogenous metastases apparently occur either through the transmission of a single or minute clump of cells, or by the formation of actual tumor emboli In both instances, as stated, tumors arise

FIG 37 A CEREBRAL BLOOD VESSEL IN THE VICINITY OF A METASTATIC NODULE FROM A BRONCHIOGENIC CARCINOMA

The vascular coat is dissociated, and the vasa vasorum are distended with tumor which also surrounds the vessel

which grow inside the vessels and also by crossing the vessel wall in the surrounding tissues (figs 37 and 38)

The rather frequent occurrence of cerebral metastases in primary carcinoma of the lungs, an occurrence which is much rarer in extra-pulmonary cancers in addition to the above mentioned factors, is favored by the absence of any barrier between the lungs and the brain A cell embolus from a pulmonary cancer, as is clearly understood,

may pass from the pulmonary vein and heart directly into the general and then through the cerebral circulation A similar embolus from elsewhere in the body on its way to the central nervous system passes primarily through the "sieve" of the lungs, the latter serving to resist the advance of the growth

As stated visceral cancers reach the lungs with great frequency The tumor emboli are, however, retained in the pulmonary capillaries where they are "immured" Moreover, frequently they lead to local

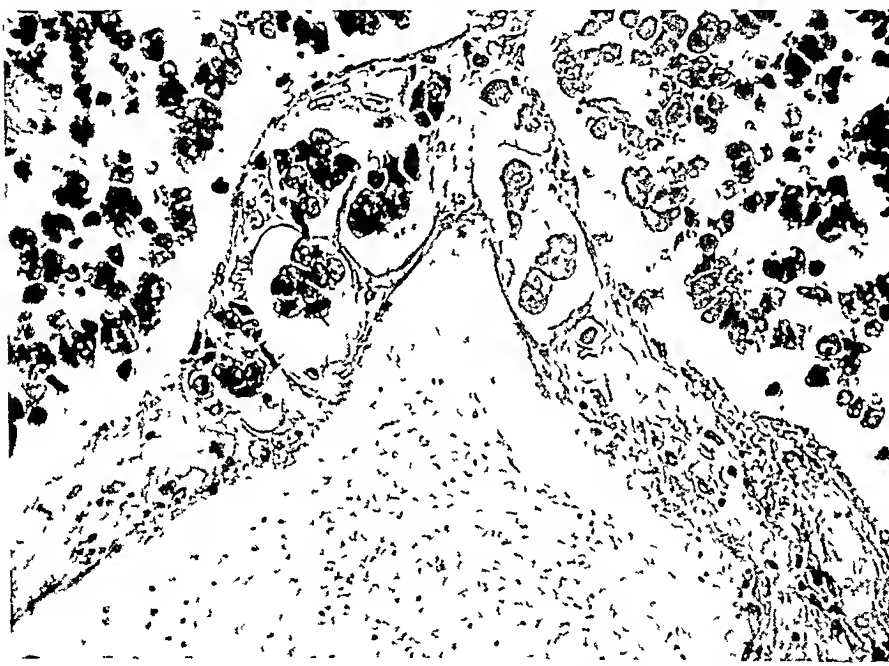

Fig 38 Showing Neoplastic Cells from a Bronchiogenic Carcinoma in the Vasa Vasorum of a Cerebral Blood Vessel

infarct formation followed by organization and destruction of the metastatic neoplastic cells

It is interesting that an abscess of the lung is more often complicated by a "metastatic" cerebral abscess than abscesses from elsewhere It is very likely then that this particular phenomenon proper to both conditions, that is, the frequent occurrence of metastases to the brain from a pulmonary abscess and a pulmonary carcinoma, is not a mere coincidence, but is due apparently to the same underlying factor—a

hematogenous transmission to the brain of a "pus embolus" analogous to the transmission of a carcinomatous "cell embolus"

The local reaction of the tissue to a metastasis is of interest That the host offers resistance to the implantation of a cancer and also to metastases has been noted The resistance was believed by one group of observers to lie in the "body fluids" (Humoral theory) and by an-

FIG 39 MULTIPLE METASTASES TO THE CEREBRAL HEMISPHERES FROM A CANCER OF THE BRONCHUS

T = tumor The invasion of the left thalamus by cancer must be noticed

other in the "body cells" (Cellular theory) Murphy and his assistants, who contributed largely to this subject, affirmed that the "small lymphocyte" plays the defensive role against the propagation of cancer in the body, while other observers attributed this to the macrophage In the material studied the reaction of the visceral organs toward the bronchiogenic cancer did not differ from that of other cancers being

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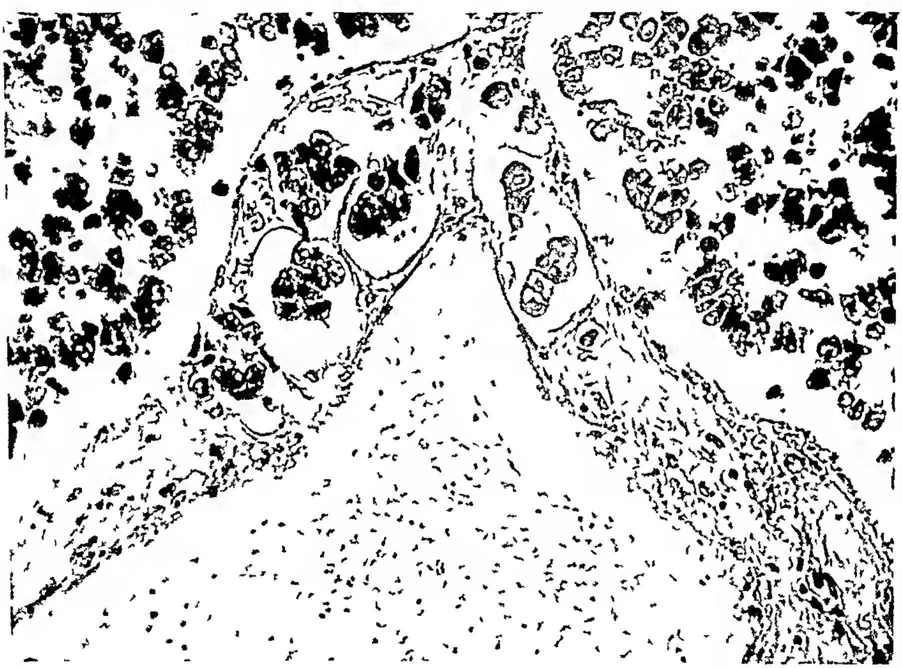

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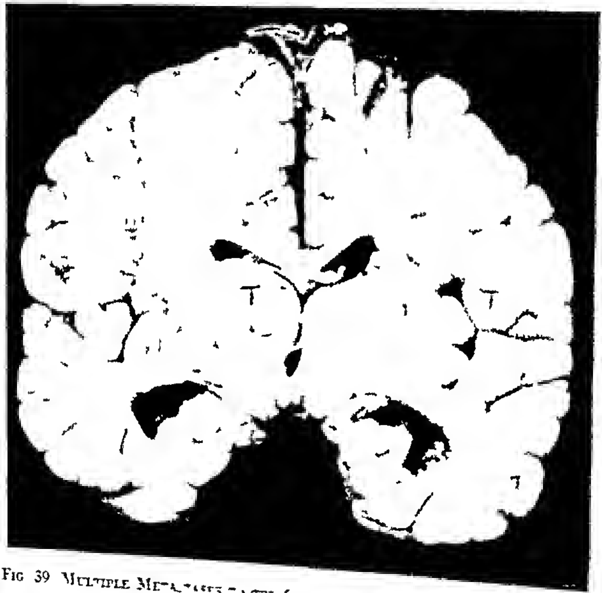

FIG 39 MULTIPLE METASTASES [illegible]

T = tumor [illegible]

other in the "body cells" (Cellular theory). [illegible] ants, who contributed largely to this subject, [illegible] lymphocyte" plays the decisive role against the [illegible] in the body, while other observers attributed [illegible] In the material studied the reaction of the [illegible] bronchiogenic cancer did not differ from that [illegible]

essentially of the lymphocytic variety In the brain where the early response of the cerebral substance toward metastases was investigated the reaction was the most interesting and merits description in some detail

The metastases (figs 39 and 40) were located in eleven instances in the motor area and in two in the occipital region In two other patients gross involvement of the leptomeninges of the cerebrum and spinal cord was seen

The secondary cerebral tumors were either firm, solid, enucleable masses up to 5 cm in diameter or large enucleable cystic masses or necrotic, broken down lesions In two cases there were single apparently enucleable nodules

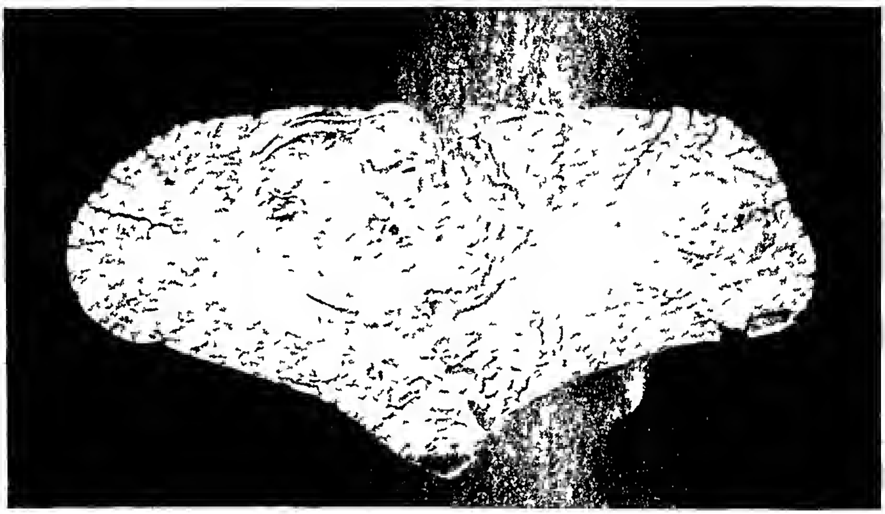

FIG 40 METASTASES TO THE CEREBELLUM FROM A BRONCHIOGENIC CANCER

5 cm in diameter In three cases there were from six to twelve nodules of varying sizes located on the same side of the brain in each instance In a number of cases the brains appeared literally riddled with about one hundred separate masses, each of the same gross appearance The brain was markedly edematous in every case studied

All elements of the cerebral substance responded to the neoplastic invasion The macrophages and the microglia (which are nothing else than macrophages), and also the transitional forms of these cells formed dense masses in the vicinity of the tumor (figs 41, 42, 43 and 44) The tumor mass itself showed, however, no penetration by the phagocytic cells, nor were individual tumor cells phagocytosed by these cells or by their deriva-

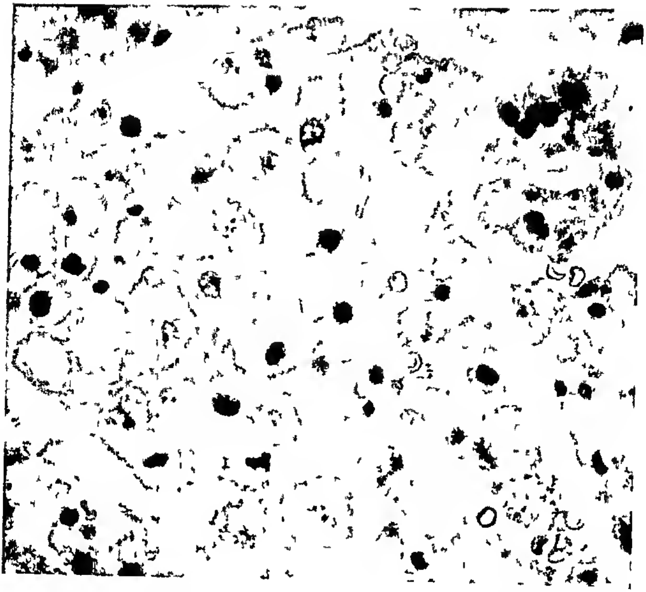

FIG 41 MACROPHAGE REACTION IN THE VICINITY OF A SMALL TUMOR NODULE, × 600

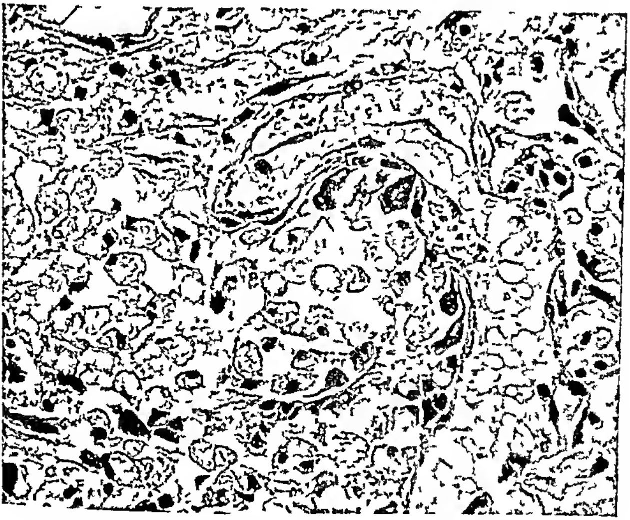

FIG 42 WIDE AGGLOMERATIONS OF MACROPHAGES NEAR A CARCINOMATOUS METASTASIS × 320

tives Large phagocytic cells were likewise seen attached to and lying free about the adventitia of small blood vessels at the boundary of the tumor and the necrotic cerebral tissue

There was a marked glial proliferation and also there was a "stream" of astrocytes all seeming to "go" in parallel rows toward the injury (fig 44)

The oligodendroglia showed swelling but no phagocytosis (fig 45)

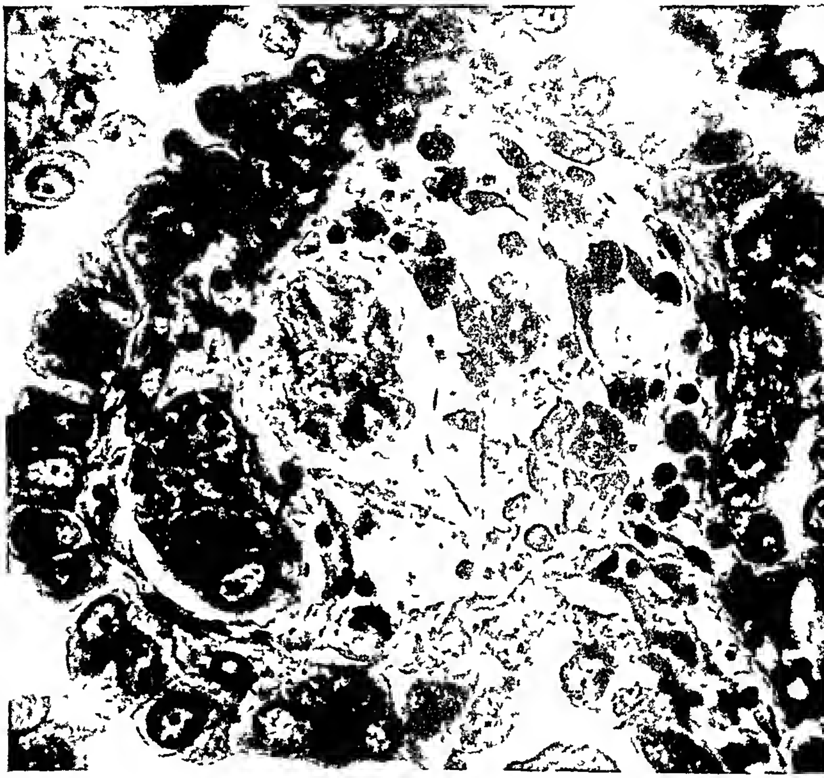

Fig 43 Macrophages (Foam Cells), Lymphocytes and Glia Cells Surrounded by a Collar of Neoplastic Cells, × 600

The nerve fibres showed complete destruction in the vicinity of the metastatic nodules In areas remote from the lesion, demyelinization, swelling and fenestration of these structures was conspicuous There also was serious damage of a toxic nature of the ganglion cells, and of the astrocytes as evidenced by clasmatodendrosis (fig 47)

The reaction described is of interest in connection with the experimental inoculation of cancer Murphy and Sturm found that trans-

plantable mouse tumors grew actively when inoculated into the brains of rats, guinea pigs, and pigeons, whereas subcutaneous or intramuscular grafts in the same animals failed They also noted that grafts of spontaneous tumors failed to grow in the brain even when the tumor implanted and the animal host were of the same species More

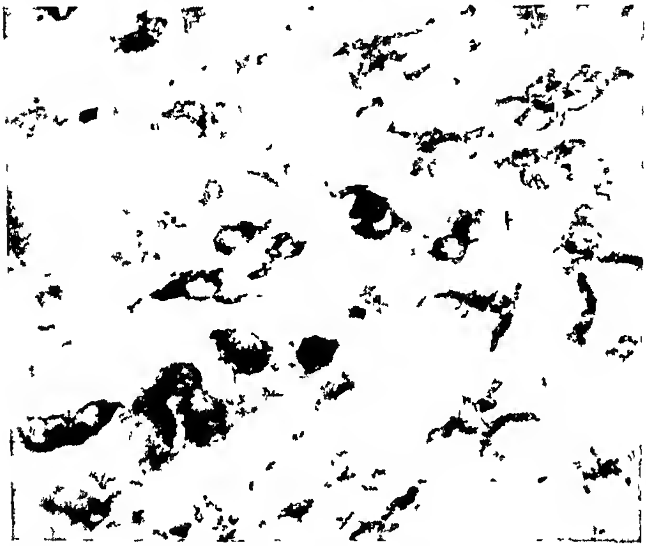

FIG 44 THE REACTION OF MICROGLIA TO THE METASTASES FROM A BRONCHIOGENIC CARCINOMA

In the right upper segment of the picture, the microglia show swollen processes In the center, the processes are shortened and thickened while in the left lower segment, the cells are seen as compound granular corpuscles Penfield's combination method for oligodendroglia and microglia, × 850

recently Lewin stated that the brain represents an "indifferent nonspecific nutrient medium" for heterologous tumors It will be seen that in the human material the reaction displayed by the brain toward cancerous metastases was rather outstanding involving all elements of the brain In general it resembled that described by Hortega and

by Penfield in experimental cerebral wounds and also in infectious processes

To summarize The phenomenon of metastasis represents apparently "an expression of the interaction between tumor and host"

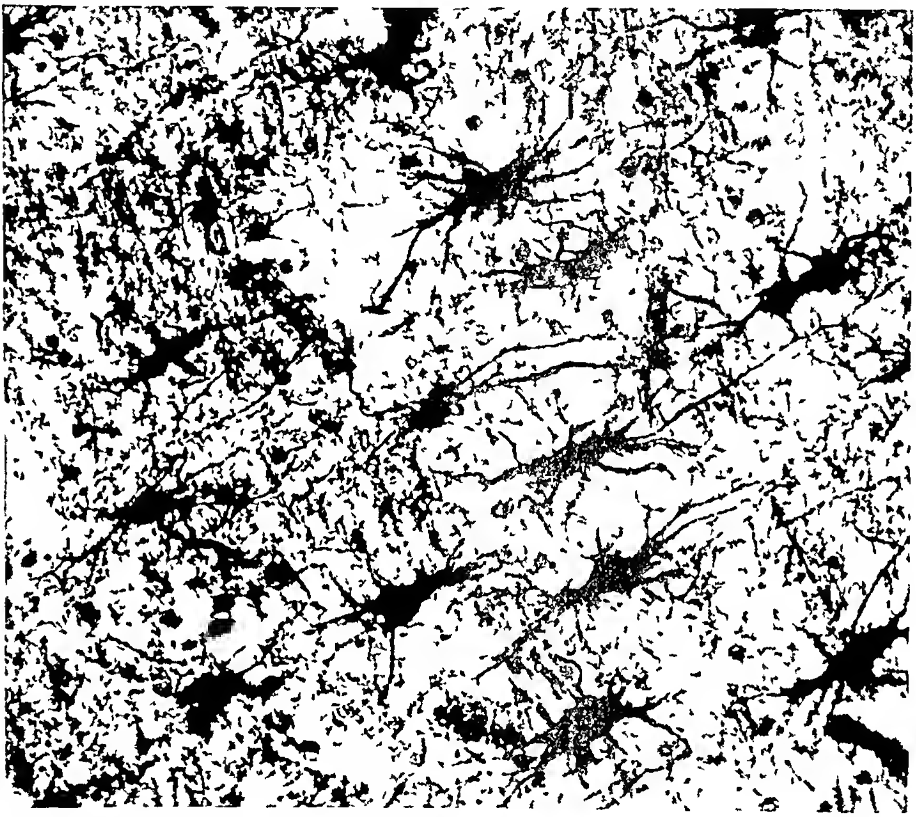

FIG 45 THE REACTION OF FIBRILLARY ASTROCYTES IN THE VICINITY OF A CEREBRAL METASTASIS FROM A PRIMARY CANCER OF THE LUNG

There is a proliferation and an increase in size of these cells Their arrangement in parallel rows gives the impression that they are "streaming" toward the lesion Gold chloride sublimate stain (Globus modification), × 320

The frequency of metastases in bronchiogenic cancer in man diminishes with the distance from the central axis of the body

Metastases from a primary carcinoma of the lungs to distant organs and particularly to the skeleton and to the central nervous system are as a rule hematogenous in character

The earliest osseous metastases occur in the center of the bones within the marrow cavities wherefrom they reach the periphery

The frequent occurrence of cerebral metastasis from primary pulmonary cancer is favored by the absence of a barrier between the lungs and the brain Metastases from elsewhere in the body on their way to the central nervous system pass primarily through the "sieve"

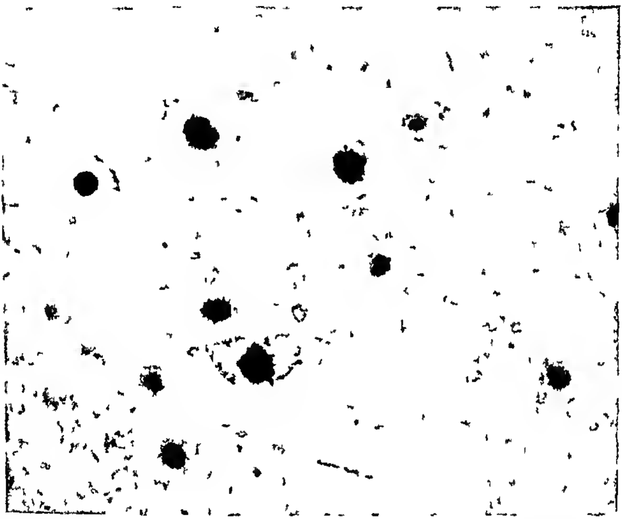

FIG 46 SWELLING OF OLIGODENDROGLIA IN THE BRAIN WITH METASTASES FROM A BRONCHIOGENIC CARCINOMA, STAIN SAME AS DESCRIBED UNDER FIGURE 45

of the lungs in which they are usually "immured" and not infrequently perish

There is a marked reaction (progressive and regressive in nature) on the part of the macrophages (and microglia) and astrocytes to the metastatic lesion, the response being very much like that found in experimental studies on the reaction of the brain to wounds and to infectious invaders

VI DURATION

The problem of the duration of a cancer is of interest not only from the clinical point of view but from the biologic From the biologic standpoint it is important to ascertain whether an epithelial malignant disease is a malady of old age *par excellence*

Observations on the mortality from cancer show that it occurs as a rule in people past middle age, namely at or above the age of fifty

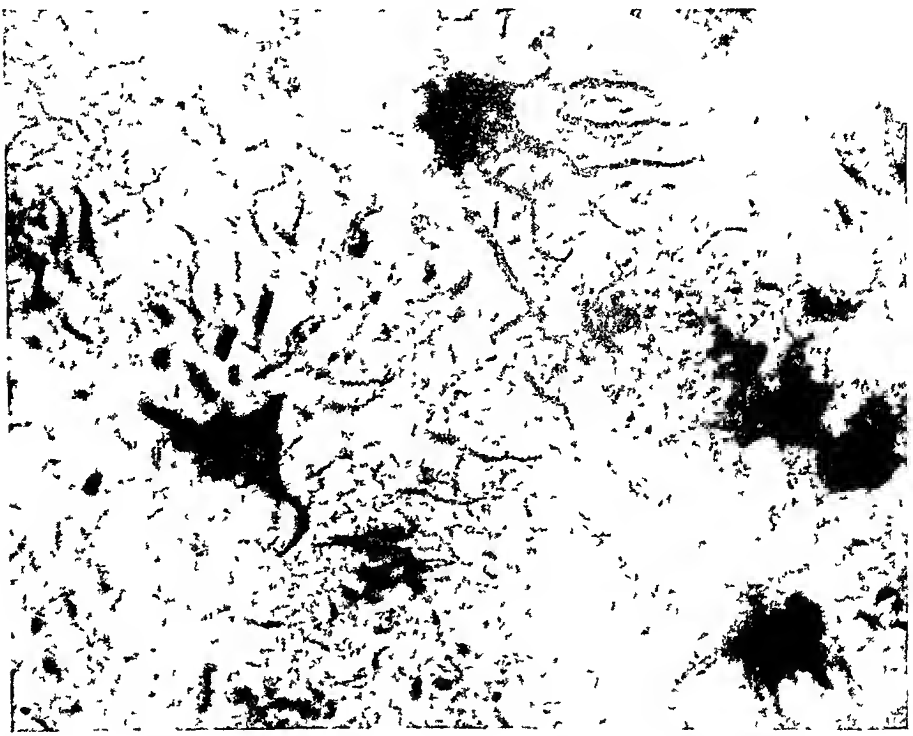

Fig 47 Clasmatodendrosis in the Vicinity of a Metastasis to the Brain from a Primary Carcinoma of the Lung, Stain Same as Described Under Figure 45

If one is to accept the view that the disease is rapidly fatal, causing death within a period of one or two years, one must also accept the notion that the condition is virtually connected with advanced age

However, the clinical course of a malignant epithelial tumor does not coincide with the virtual existence of the disease the interval between the inauguration of the neoplasm and the appearance of symptoms passes usually unnoticed and as a result the duration of

the process cannot be determined Thus Ewing (1929) stated that "many cancers appear in old age, not because they are the result of any element of senescence, but merely because the lapse of time allows the fruition of processes which have their inception at a much earlier period" Likewise Blumenthal by investigating in the Cancer Institute in Berlin a series of accessible or easily diagnosticated cutaneous cancers, observed that the period between the inception of a skin lesion and the appearance of a clinically recognizable cancer oscillated between one and ten years The author, too, is opposed to the view that cancer is a "monopoly" of the aged

In this connection it is of interest to note that the "latent" period in experimental cancer of the mouse is from 6 to 8 months which is nearly one third of this rodent's span of life Bang and others called attention to the fact that in chimney sweepers and in the aniline and paraffine workers cancer usually develops in from 20 to 30 years after they have changed their occupation, that is after the irritant has been applied This would indicate that in man, too, one third of his life is required for a cancer fully to develop

Clinical reports are to the effect that pulmonary cancer runs a rapid course causing death of the patient in a period varying from three months to about two years Thus in a study of twenty-six patients with pulmonary neoplasms Hunt stated that "it is difficult to believe that the average total duration (of the disease) can be more than two years"

It is, however, most likely that bronchiogenic cancer (probably most cancers) is a chronic condition running as a rule a course over a period of several years The fact that the clinician estimates the duration of the process as being about two years merely indicates that the disease as such is recognized in the clinic late, possibly at its terminal period

From the three examples to be cited it will be seen that even in those patients who have been operated upon for the removal of a cerebral metastasis from the lung the survival was longer than clinical reports would lead one to expect In one instance the patient lived seven years after the onset of the first symptoms during which period he underwent two intracranial and one abdominal operations Two other patients each survived about three years after the removal of the intracranial metastasis The patients' histories are as follows

Case 1 (P B B H No 63455) Onset sudden in 1922 with right hemiplegia and aphasia Cranial exploration with removal of malignant epithelial tumor from left motor area primary source not determined Recurrence of symptoms six months later followed by second cerebral exploration resulting in complete recovery Disclosure of bronchiogenic cancer in 1928 regarded as the source of the cerebral tumor removed in 1922

History H S , a Jewish merchant, aged seventy years, entered the hospital for the fourth time complaining of pain in epigastrium, in right arm and also in the intercostal region Three months before he had begun to have a constant dull pain in the midepigastrium and sometimes about the umbilicus, radiating over the lower two ribs anteriorly, continuing to their vertebral attachments There was present also a marked hyperesthesia over the lower right intercostal spaces At the same time he had an excessive cough productive of considerable dark sputum, usually streaked with dark blood but there was no frank hemoptysis He also developed dyspnea on slight exertion and even at rest For the past two months he had suffered a constant dull pain in the right arm beginning at the elbow joint and radiating to the finger tips Later it had appeared at the back of the neck and radiated down the arm He had lost eighteen pounds (about seven kg) in weight in the past six months

Previous admission to the hospital The patient had first entered the hospital in December, 1922, with the complaint of incoordination of speech and paralysis of right arm and leg of six months duration, with nocturnal headaches and paresthesia over scalp Examination showed a choked disc, hemiparesis, hemi-hyperesthesia, hyperactive reflexes on the right side, right facial weakness, aphasia, apraxia, and inability to carry out complicated commands The systolic blood pressure was 170 and the diastolic 86 A diagnosis of a tumor of the brain was made

Following an intracranial intervention a nodular tumor was removed from the posterior end of the sylvian fissure which was diagnosed as a metastatic carcinoma The patient made an uneventful recovery and was discharged practically free from any cerebral symptoms

About six months after discharge from the hospital (June, 1923) the patient had a recurrence of previous symptoms Examination showed motor aphasia, a slight facial weakness, a right hemiparesthesia, an exaggeration of tendon reflexes on the right, also a secondary optic atrophy The impression was that there was probably another tumor nodule involving the inferior half of the fissure of Roland on the left side The old bone flap was then re-elevated and a tumor nodule weighing 42 grams was removed The patient was discharged twenty-one days after the operation

with only a slight weakness of the small muscles of the right hand and some stuttering

He has been reexamined in December, 1925, and no disease was found He had remained well until about September, 1928, when he was readmitted to the hospital for the repair of an incarcerated femoral hernia While in the hospital a study was made to find out the source of the metastatic cerebral lesion removed six years ago

Examination The patient was well developed, poorly nourished and dyspneic, lying restlessly in bed and coughing a great deal His face showed general cyanosis with flushing over the molar prominences The pupils were irregular but there were no synechiae The voice was slightly hoarse The thorax was of the emphysematous type with an increased antero posterior diameter The respiration was asthmatic

The lungs showed dulness over the upper half of the chest posteriorly extending to the axilla and the angle of the left scapula as well as both bases posteriorly Breath sounds and tactile fremitus were diminished in these areas The whispered voice was slightly increased in the left upper chest anteriorly The respiration here was bronchovesicular Râles were also heard over this area The rest of the lung showed hyperresonance The heart was negative The blood pressure was systolic 110 and diastolic 50 The liver was enlarged and tender The prostate showed enlargement but no irregularities or nodules The spine showed a marked kyphosis

The laboratory findings were of no importance

Roentgen-ray examination of the gastro intestinal and the genito-urinary tracts showed no disease Stereoscopic roentgen-ray examination of the lungs showed a shadow in the left upper lobe corresponding to the pathologic changes found the clinic

Following discharge the patient lost weight rapidly His cough became very distressing and his sputum was blood tinged He complained of severe pains in the intercostal region and in the right arm He was then readmitted to the medical service where clinical and roentgenologic studies showed a diffuse involvement of the left lung by a solid tumor

He was transferred to the Palmer Memorial Hospital with diagnosis of bronchiogenic cancer, metastatic to brain and bones, chronic myocarditis, and benign hypertrophy of prostate A few days after discharge he died

The patient presented a most interesting problem He had had two metastatic nodules removed from the left motor area more than seven years earlier A primary tumor was never found to explain this Tumors that metastasize more commonly to the brain are chordomas

either of the clivus or the sacro-coccygeal region, tumors of the prostate, occasionally tumors of the stomach, pigmented malignant tumors, some bone tumors and above all bronchiogenic cancer The prostate could be ruled out it seemed to be of the same size and consistency as at previous examinations A roentgenologic examination of the gastro-intestinal tract was negative There were no areas of pigmentation over the body and the sacro-coccygeal region showed no changes whatsoever It appeared then beyond reasonable doubt that the two malignant epithelial nodules removed in 1922 had reached the brain from the lungs, where a tumor was localized by the roentgen-rays and by clinical methods

Previous to the clinical evidence in 1928 of a carcinoma of the lung various diagnoses were made from the slides, notably a metastatic chordoma or a hypernephroma Having the opportunity of studying a large number of sections of metastatic cerebral lesions, especially from pulmonary tumors, the author is convinced that the cerebral neoplasm in this patient took its origin in the lungs

Here, then, is an example of the survival of a person for nearly seven years after the removal of a cerebral lesion which had metastasized from the lungs It is interesting that at the time when the patient was operated upon in 1922, the idea that the lungs might have been the source of the lesion did not occur to the personnel of the hospital For the last few years at the Peter Bent Brigham Hospital it has been a custom to examine the thorax with the roentgen-rays in every instance of a cerebral tumor with an atypical history This case is of further interest in connection with the advisability of an intracranial exploration in instances when the lesion in the brain is *a priori* known to be a metastasis

Case 2 (P B B H No 55905) A patient with attacks of Jacksonian epilepsy of the left hand Osteoplastic operation with removal of a metastatic nodule from the right parietal lobe Subsequent disclosure of a carcinoma of the lung Death two years later

History A Canadian physician aged sixty-four whose past and family history was irrevelant entered the hospital March 18, 1927, complaining of epileptic attacks associated with numbness of the left hand, of three and one-half months duration The result of the examination can be summarized as follows

A Subjective (1) a persisting numbness of three and one half months duration of the left hand with loss of power of appreciating objects, (2) four attacks of Jacksonian epilepsy of the motor type in the left hand and in the left side of the face (3) mental change evidenced by slight failure of memory and power of concentration, (4) slight occasional incontinence of sphincters in the past six weeks

B Objective (1) an early choking of discs, (2) slight left sided weakness, a left lower facial weakness and defect of synergistic movements of the left

Fig 48 Case 2, A Roentgenogram Taken About Two Years Before the Patient Died

hand (3) a left sided Babinski, absence of left upper abdominal reflexes, (4) astereognosis of left hand, slow reaction time and slight loss of concentration power and memory

The impression was that there was probably a tumor situated in the region of the right Rolandic fissure The inconspicuousness of the pressure signs and the abruptness of onset made it possible that the new growth was metastatic, although no clinical evidence of any primary focus was detected

March 30, 1927 The patient was operated upon by Dr Cushing and a tumor nodule 3 cm in diameter lying in the upper portion of the post-central convolution was removed It was thought that this small lesion could not account for all of his symptoms, and that there were certainly metastases in other parts of the hemisphere The histology of the tumor was that of cancer, probably metastatic from the lungs

FIG 49 CASE 2, METASTASES TO THE BRAIN FROM A BRONCHIOGENIC CARCINOMA

The insert shows a section through the old operative site to show the recurrence of a metastasis two and one half years after the operation The central part of each nodule is necrotic The brain was distorted in transportation

Roentgen-ray examination A stereoscopic examination of the chest showed at the left base a triangular area of increased density toward the axilla, and some fibrosis and calcification medially This suggested to the roentgenologist as possibly being an old inflammatory process, an interlobar pleurisy, or a bronchiogenic cancer (fig 48)

The patient was discharged improved

April 8, 1927 At home he continued to improve and regain much of his

former activity for eighteen months, but in September began to fail again In the next six months there was a gradual failure (without any conspicuous pulmonary symptoms) until death occurred in April, 1929, a little more than two years from the date of his cranial operation

Necropsy This was limited to the head A series of thin coronal sections of the brain revealed three large typical metastatic nodules Two were symmetrically located in the posterior part of the frontal lobes just below the corpus callosum They each measured about 3 cm in diameter At the site of the previous operation there was a large metastasis 5 cm in diameter The nodules were well demarcated, their centers were opaque and necrotic, white, the borders consisted of a pinkish-red translucent tumor tissue (fig 49)

The time interval between the inauguration of the bronchial tumor and the occurrence of the cerebral metastasis is naturally unknown One is unaware likewise as to the time which has elapsed between the lodgment of the cancer in the brain and the appearance of cerebral symptoms It is certain, however, that when the patient entered the hospital the primary new growth of the lung and the secondary tumors in the brain were of considerable size Yet the patient lived more than two years after the intracranial exploration had taken place

In the case to follow the patient, a younger person, was operated upon twice for the removal of a metastatic cerebral lesion with a still longer survival

Case 3 (P B B H Surg No 30684) Gradual onset with headaches, loss of strength and loss of vision Right facial weakness Osteoplastic exploration with removal of large cystic tumor Histologic diagnosis Metastatic epithelial tumor Roentgen ray disclosure of a bronchogenic carcinoma Recurrence of symptoms followed by a secondary operation twenty months later with removal of a large cyst Recovery Sudden death from pulmonary embolus two weeks after the operation

History On April 6, 1925, Mrs G, a Jewish housewife, aged forty-six years, was admitted to the medical service with a complaint of severe headaches The onset of the present illness had been sudden, five months before admission Soon there was a gradual loss of vision and strength

Examination There was evidence of slight loss of weight A right facial weakness and bilateral choking of the optic discs were the only other positive findings

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Examination There was evidence of slight loss of eyesight A right facial weakness and bilateral choked discs were the only other positive findings

Course of illness The patient was considered as having a tumor of the brain and was transferred to the surgical service A ventriculogram demonstrated a block of the left foramen of Monro and a multicystic tumor in the left occipital lobe

On April 25, 1925, Dr Cushing performed a left occipital exploration and removed a cystic tumor The fluid in the cyst was mucoid, yellow and contained cholesterin crystals, fat and macrophages The microscopic sections showed a carcinoma probably of bronchiogenic origin

FIG 50 CASE 3, A ROENTGENOGRAM TAKEN ABOUT TWO YEARS BEFORE THE PATIENT'S DEATH

The chest was then examined by Roentgen-rays and revealed the presence of a tumor in the hilum of the right lung (fig 50)

The patient made an uneventful recovery and was discharged improved

Interval history The patient was seen at intervals in the next two years One year after the operation there was distinct clinical evidence of a cerebral embolus, the effects of which gradually wore off At times there was some evidence of a pleurisy on the left side and occasional hoarseness

February 18, 1928, symptoms of intracranial pressure recurred and she

was readmitted to the hospital Roentgen ray examination of the lungs showed a shadow in the left hilus which was slightly increased in size as compared with the first examination A careful search for a neoplasm elsewhere of the body was negative

February 22, a second exploratory operation was performed and a cystic tumor removed from the same location as that of the first tumor (fig 51)

The patient was making normal recovery when death due to a pulmonary embolus occurred on March 6, 1928, about three years after the onset of the cerebral symptoms

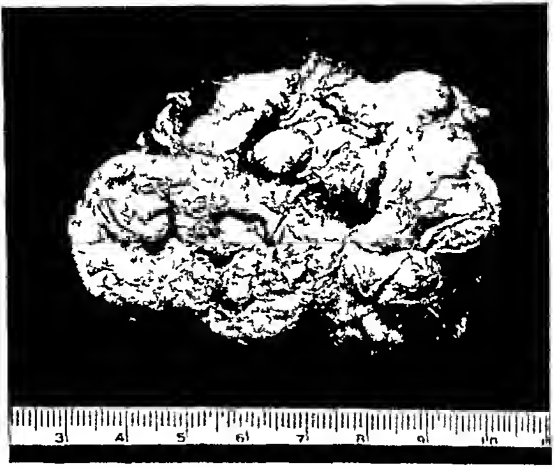

FIG 51 CASE 3, A CYSTIC METASTATIC TUMOR FROM A PRIMARY CARCINOMA OF THE LUNG REMOVED AT A SECOND OPERATION PERFORMED TWO YEARS AFTER THE FIRST OPERATION

Microscopic examination The first specimen removed in 1925 from the left occipital lobe consisted of a multilocular cystic mass about 5 cm in diameter It contained over 30 cc of dirty, orange colored fluid, the examination of which disclosed macrophages, cell debris and many cholesterin crystals The wall was thin and local thickenings of gray-white tissue represented mural nodules of tumors

The second specimen, removed in 1928 from the same location as the

first cyst described above, consisted of a large oval cyst measuring after fixation 9 by 6 cm and containing more than 75 cc of a material similar to that found in the first specimen This large cyst had a thin, transparent wall and contained one large mural mass of gray-white tissue about 3 cm in diameter and 2 cm in height

Sections of the metastasis removed in 1925 and in 1928 were available for study The histology of the tumor is briefly as follows There is an abundance of mucoid material and crystal spaces such as are made by cholesterin crystals The tumor cells in both specimens are low cuboidal arranged in thick strands of alveoli There are relatively few mitoses The nuclei are less hyperchromatic and the cells appear to be smaller in the specimen removed in 1925 than in the last specimen

The patient in this case lived three years after the first cerebral exploration with the removal of a tumor, and more than three and one half years after the onset of the cerebral symptoms As said in the introductory paragraphs the natural history of a bronchiogenic cancer cannot be estimated It is, however, apparent, that as a rule it runs a protracted course of many years

VII DIAGNOSIS

The diagnosis of a carcinoma originating primarily in the lungs is based on (1) Clinical findings which are made up of the history, the symptomatology and the physical signs, (2) Laboratory findings gathered from the examination of the expectorated material and the pleural exudate, and also from bronchoscopic and roentgenological examinations

CLINICAL FINDINGS

The history

The history of a patient with a bronchiogenic cancer as a rule lacks data suggesting an etiological relationship between his past life and present illness This amazingly "silent" anamnesis is of interest in connection with the "irritation" theory of cancer. It is believed by many that the "irritation" preceding this malignant disease must necessarily be of some magnitude, such as bronchiectasis, pulmonary syphilis, tuberculosis or other chronic suppurative conditions of the broncho-pulmonary tree In reality an appropriate "stimulus" of

microscopic dimensions when applied for a certain length of time will lead in a receptive individual to the development of a malignant condition "*Gutta cavat lapidem non vi sed saepe cadendo*" may aptly be said about the initiation of a cancer The *ante cancerous* history, of a malignant neoplasm of the lung, probably as that of most cancers, will then be of no avail in elucidating the present condition of the patient Moreover, as already emphasized, even in the early stages (and it is not known how long they are) the pulmonary lesion is often not heralded by any outstanding subjective signs, thus keeping the patient in ignorance as to the virtual onset of his illness

Classification

The older clinicians (Adler, Osler) discriminated two varieties of pulmonary cancer an acute galloping pleuropulmonic form, said to run a rapid course of from six to twelve weeks, a chronic pleuropulmonary form

More recent observers (Fried, 1925), being impressed with the frequent occurrence of early metastases in this condition and also with the fact that in these patients most of the symptoms result from the secondary growth, have ventured to classify the disease arbitrarily into two main groups

1 Typical, including patients whose chief complaints pointed toward the thoracic organs

2 Atypical with symptoms and signs directed toward a metastasis

ILLUSTRATIVE "TYPICAL" CASES

Case 4 Onset of illness with cough and pain in chest, regarded as pulmonary tuberculosis Death Necropsy disclosure of a bronchiogenic cancer

History W S, an American born man, aged fifty-two, was admitted to the Boston Sanatorium, July 8, 1922, with the chief complaint of cough and pain in the back and the left side of the chest for the last six months The past and family histories were irrelevant

Present illness Six months before admission the patient had begun to have pain in the back and left side of the chest, at first sharp, later dull, the pain was intermittent, lasting for about twenty minutes, and was worse on lying down, not being related to meals or micturition At the same time he had developed a cough productive of a moderate quantity of thin, white, mucoid sputum streaked occasionally with blood In March he had a hemorrhage,

coughing up one third of a glass of bright red blood Before entering the hospital, the patient had gone to several clinics and in April, 1922, was admitted to the Massachusetts General Hospital His record while there was as follows

FIG 52 CASE 4, BRONCHIOGENIC CANCER, ROENTGENOGRAM TAKEN ABOUT THREE MONTHS BEFORE THE PATIENT DIED

The dense shadow in the right is due to the fibrosed lung infiltrated by tumor and to a hydrothorax The gross appearance of the right lung is given in figure 23, p 429

April 3 The history of hemoptysis seemed definite, and suggested tuberculosis strongly He had lost little weight, and had few pulmonary symptoms The right side of the chest showed an increased whispered voice at the apex, but no râles were heard The sputum had been blood streaked

April 4 Fluoroscopic examination revealed that the upper half of the left chest showed a marked decrease in radiability, apparently with a sharp lower border about the interlobar septum The trachea and the heart were displaced to the left The left diaphragm was fixed The left apex did not light up The right side showed considerable mottling around the root beneath the clavicle, otherwise, it was clear The right diaphragm moved normally The posterior mediastinum was obscured These changes probably represented an extensive destructive and fibrosing process in the right upper lobe with retraction of the mediastinal contents to the affected side On the left, the fine mottling suggested small bronchopneumonic areas (fig 52)

April 5 Clinically, the signs suggested fibrosis of the right apex with shrinkage, while the right clavicle was thrown out There was distortion of the spine Syphilis was excluded There seemed to be no evidence of a new growth It appeared that there had possibly been some chronic interlobar infection The diagnosis of chronic fibroid pulmonary tuberculosis was finally made

April 9 The patient was discharged to his local physician

July 8, 1922 Physical examination at the Boston Sanatorium showed the patient to be well developed but poorly nourished The skin was dry and not jaundiced The upper part of the chest in front was covered with tinea versicolor The heart was negative In the lungs, the left apex was moderately dull, with a few fine rales, in the right, there was dulness and bronchial breathing from the apex to the inferior angle of the scapula, with increased voice sounds Below, to the base, there was flatness and a complete absence of breath sounds In the abdomen, the liver was felt 10 cm below the costal margin with a slightly tender and somewhat nodular edge The genitalia were negative The prostate was not enlarged or painful on palpation In the bones, there was right lumbar scoliosis

July 12 The patient was tapped, and 900 cc of straw colored fluid was withdrawn from the right pleural cavity

The urine and stools were negative The sputum was negative for tubercle bacilli on six examinations The clinical diagnosis was pulmonary tuberculosis

The patient died after nine weeks in the hospital

The necropsy revealed a right bronchiogenic cancer with metastases to the left lung, liver and rib, right hemothorax and sclerosis of right lung (figs 23 and 53)

Case 5 (B I H No 1200) Onset gradual with pain in chest Disease of the heart, and pulmonary tuberculosis suspected Death about four years after onset of symptoms Diagnosis Bronchiogenic cancer

History P F, a married Jewish antique dealer, aged fifty-six, who had come to this country from Russia several years earlier, was admitted to the Beth Israel Hospital, Boston, January 15, 1929, with the complaint of pain in chest His family history was irrelevant Except for a "bronchitis" off and on for the last fifteen or twenty years, the patient had been

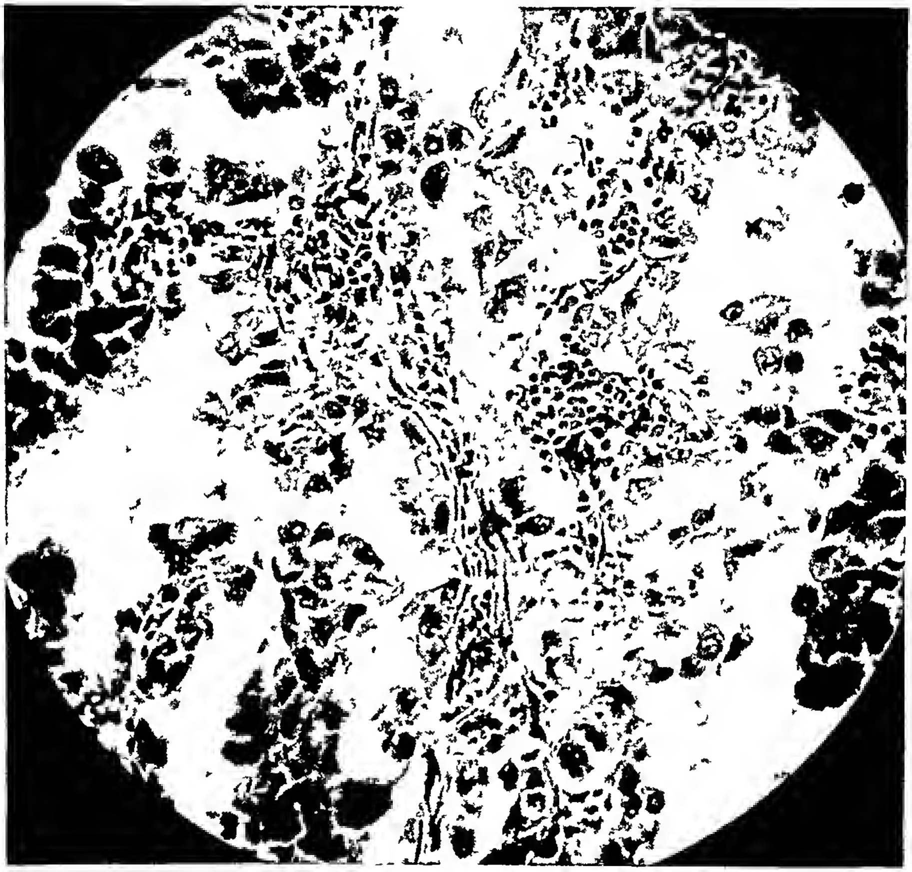

FIG 53 CASE 4, THERE IS THICKENING AND SCLEROSIS OF THE WALL OF THE AIR SAC WHICH IS INFILTRATED WITH SMALL LYMPHOCYTES

The cuboidal neoplastic cells lay singly and in masses in the alveolar lumen They also line the "naked" alveolar septums, forming papillary projections into the air sacs

perfectly well all his life He had been a heavy cigarette smoker for a number of years

Present illness The present illness began in the latter part of 1925 with a dull aching pain in the posterior upper chest just below the neck A roentgen-ray examination of the chest revealed that he had a "scar" at

the upper portion of the left lung He then consulted a competent phthisiologist who also found a "scar" in the same location but no signs of tuberculosis

He improved somewhat, but early in 1927 the disease recurred with an increased severity A local physician found some disturbance in the heart, and this was confirmed by a cardiologist who treated him with digitalis He soon lost his appetite, became weak, and the pain in his chest and cough increased During the year 1928 he consulted numerous physicians without however any result

He was sent to Colorado where an advanced tuberculosis of the lungs was found and he was confined to his bed for two months

When he returned to Boston he was again examined by several physicians who failed to recognize his condition

His complaints may be considered separately

1 Cough Although he had coughed for a number of years, that of the last two years was distressing He expectorated much thick odorless sputum He had hemoptysis on several occasions and his sputum was blood streaked

2 Dyspnea Shortness of breath progressively increased, alarmingly He felt better lying on his left side Lying on his right side caused him to cough and to vomit His dyspnea did not occur in attacks, nor did he have wheezing

3 Pain The pain in the left chest steadily increased, occasionally radiating down the left arm, at times to the back and to the shoulder Its severity kept him awake at night

4 Hoarseness This was noticed after February, 1928

5 Weight His best weight three years earlier had been 220 pounds (90 kgm) at the time of his admission to the hospital he weighed about 165 pounds (65 kgm)

6 Fever The temperature had a tendency to be elevated now and then

7 Night sweats He perspired only occasionally

Inspection revealed that his chest was markedly asymmetrical, the left side being retracted

Examination showed dulness to flatness confined to the left upper thorax extending to the angle of the scapula, the tactile fremitus was much decreased, the vocal fremitus was barely audible and the whispered voice was of the amphoric type There were no râles heard The base of the same lung was hyperresonant The right lung showed signs of emphysema The heart, the abdominal and the pelvic organs showed no disease

Stereo roentgenographic examination of the chest showed the entire left

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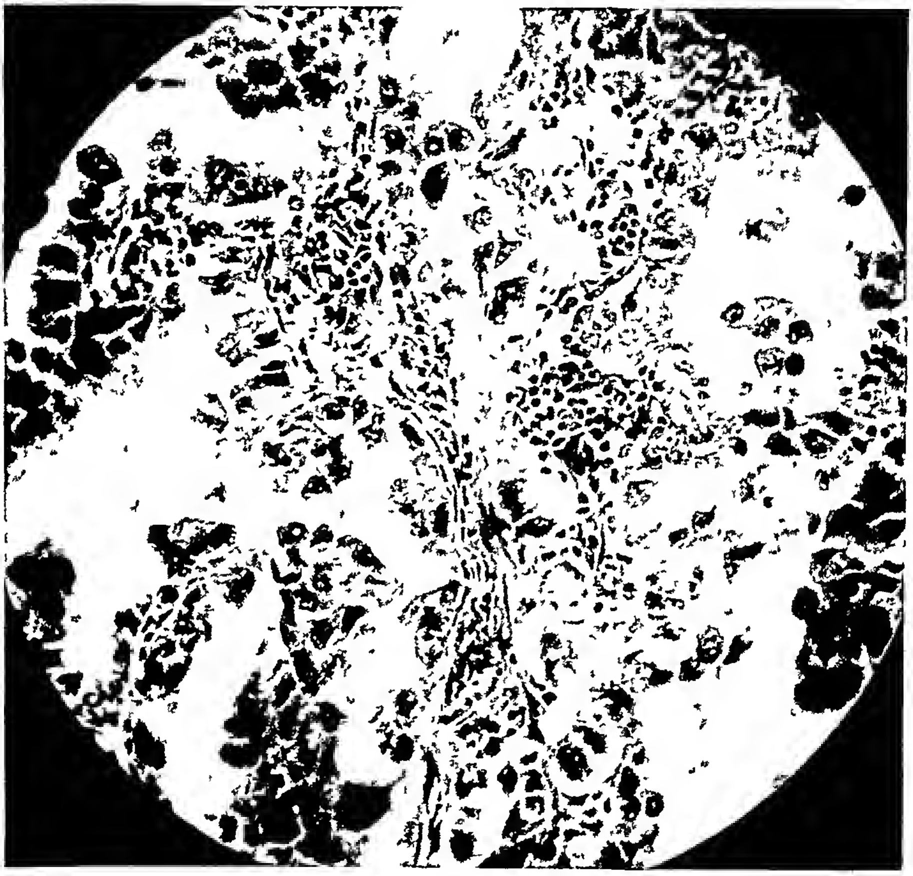

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...nt than the right. The increased density appeared to ... half of the chest. The left side of the diaphragm was ... costo-phrenic angle was hazy. The heart was displaced ... right lung showed emphysema.

... of the roentgenologist was that there was an obstructive ... bronchus probably due to a primary malignant disease of

... was discharged ten days after his admission with the diag-... carcinoma of the left bronchus

... Following discharge he developed gradually increasing ... was due to extension of the bronchial tumor upward ...pression of the oesophagus He was soon unable to swal-... which would lodge about the esophagus Vomiting became ...sing symptom. Finally he was unable to swallow even

... four years after the onset of the symptoms

... in these two patients is regarded as being "characteristic" ... chief complaints were directed toward the respiratory ..., dyspnea, and pain in chest.

...cussion to follow the symptomatology will be taken up

Physical examination

... The inspection of the thorax is of importance in the ... pulmonary tumor. Since bronchiogenic cancer is as ...l condition, the thorax shows in very many patients ... the affected side being "atrophic" as compared with ... It is possible that the impairment of the diseased ... to the inauguration of the malignant con-... stated is often preceded by some patho-... It is then possible that in some ... to a partial immobilization of ...ons with a "hemiatrophy" ... condition was caused ... in an atelectasis ...luritis ... affected side ... side, and

Dyspnea The opinion of Means that "the likelihood of intrathoracic tumors producing dyspnea seems to depend to a greater extent upon their position than upon their size" is also this writer's opinion Means cited examples in which small but centrally located or mediastinal tumors have produced the greater respiratory embarrassment However, labored breathing will also be caused by cancers which have a tendency to grow around the bronchi and blood vessels, constricting them in a ring-like manner thus interfering both with the respiration and the circulation The premature involvement of the pleura and the diaphragm may also cause shortness of breath

Dyspnea is regarded by some writers as an early symptom This may be true in the mediastinal and in the perivascular and peribronchial types of tumor, but otherwise it occurs probably not as early as suspected In fact, most observers studied their patients for no more than two years, which in the estimation of the author should not be regarded as an "early stage"

Cyanosis Cyanosis is a condition occurring in instances where there is anoxemia or a difficult transport of oxygen Loewy and Schrotter (quoted by Lundsgaard and Van Slyke) found that in normal individuals two thirds of one lung (the right upper and middle lobe of the right lung) could be shut off from aeration without causing cyanosis, whereas with the cutting off of a whole lung cyanosis ensued

In a few of the patients herein discussed in whom nine tenths of one lung was transformed into a solid neoplastic block, and the other lung showed metastases, no cyanosis occurred This was possibly due to the fact that the process was developing at a slow pace thus giving the patient time to adapt himself to the newly created condition Indeed, as in instances of dyspnea, the occurrence of cyanosis will largely depend upon the topography of the tumor and some complications, but not on its size Thus, one of our patients showed a complete block of the bronchus of the right lower lobe and partial block of the bronchi of the middle and upper lobes He was dyspneic and orthopneic with a definite asthmatic stridor on expiration, yet his cyanosis was not outstanding Another patient whose chief complaints were dyspnea and cyanosis of six weeks duration showed at necropsy a small pulmonary tumor There were, however, a hydrothorax, metastases to the pleura, pericardium, heart and liver, and a

generalized arteriosclerosis None of the "early" cases that were studied in the neurosurgical clinic for cerebral metastases showed dyspnea or cyanosis

Hoarseness: The involvement of the recurrent laryngeal nerve either by pressure or by neoplastic invasion will lead to hoarseness

Stridor This was present in one of our patients It could not be determined at which period of the disease this phenomenon occurred

Loss of weight, cachexia: The patients keep their weight for an indefinite period of time The history of loss of weight usually occurs from six months to about one and a half years before death

Cachexia is not a common finding in bronchiogenic cancers possibly because many patients succumb to some complication before this symptom occurs In instances when the clinical course is protracted it becomes noticeable about one year before death

Oedema This occurs in instances when the tumor interferes with the circulation either from without or from within by a neoplastic thrombosis Oedema may be confined to one arm, or to the entire chest In such instances there is also a dilatation of the superficial thoracic veins

Adenopathy The finding of a subclavian lymph node invaded by tumor, so characteristic of gastric cancer (usually the left), is uncommon in bronchiogenic cancer Inguinal and axillary adenopathy is a rare finding in pulmonary cancer

Fever and night sweats A mild fever is not rare In many instances it probably results from a pulmonary infection engrafted upon the tumor

Night sweats occur in some cases of primary carcinoma of the lung

Inequality of pupils: This phenomenon seen occasionally in bronchiogenic cancer is due to paralysis of the sympathetic nerve involved by either the new growth or an early malignant or inflammatory apical pleuritis

Cough: It is difficult to estimate how soon after its appearance a bronchiogenic tumor leads to a cough It seems likely that signs of bronchial irritation occur rather early in the course of the disease, but proper attention is not paid to them by the patient or by the physician In a few of our patients a persistent cough or other pulmonary disturbances had been for years regarded as "bronchitis" and "asthma"

In some of them the tumor was recognized at a later period, the preceding cough being interpreted as the "previous longstanding chronic inflammation" which had led to the inauguration of the neoplasm It is, however, possible that this symptom did not antedate the cancer but was caused by the malignant disease itself Cough was present in 90 per cent of Fishberg's patients It was an outstanding symptom in many of our patients who came to the clinic, say, one to two years before their death Patients admitted to the hospital for a cerebral or skeletal metastasis always denied having had cough However, a close observation often revealed a peculiar grunt, or virtually a superficial, dry cough which had been unnoticed by the patient It is also true that in a few instances in the presence of a sizable tumor (4 or 5 cm in diameter) in the lung no signs of bronchopulmonary irritation could be elicited ("occult" tumors)

Cough, or a peculiar grunt, is then characteristic of the disease, occurring probably in its incipient stages

Expectoration The expectorated material is mucoid or mucopurulent, this being often intimately mixed with blood Blood-tinged or "rusty" sputum often appears before most other subjective or objective symptoms A frank hemoptysis (as a rule a teaspoonful in amount) occurs later in the course of the disease This symptom, too, is either overlooked or regarded as being due to an acid fast infection, or to disturbances in the upper respiratory tract

Pain Patients with pulmonary cancer often complain of pain in the chest, in the extremities or in the bones Not infrequently this complaint represents the leit motiv of the history This has been observed by previous writers (Wolf, Adler), and more recently emphasized by Fishberg and the author It is commonly agreed that thoracic pain is an early sign in primary carcinoma of the lung, and that no other disease will lead to such a persistent, sharp, stabbing pain with failure to respond to treatment

The intimate mechanism of the origin of pain in serous membranes in general and that of the lungs in particular has been the source of multiple investigations with, however, discordant results By one investigator it has been attributed to increased friction caused by a roughening of the pleural surfaces by the inflammatory exudate, by others it has been connected with the tonic contractions of the hyper

sensitive intercostal muscles. Experiments by Capps have shown that the visceral pleura does not respond with a painful sensation when irritated by touching with a wire point, while the parietal exhibits a prompt response to stimulation Capps believes that an anterior mediastinitis by involving the parietal pleura causes direct local pain, aggravated by inspiration, and with tenderness on pressure A posterior mediastinitis, too, involving the parietal pleura leads to dorsal pain. Bray considers that "the cardinal feature of the (pleuritic) pain is due to tension of the inflamed parietal pleura."

In pulmonary cancer pain in the chest may also be due to involvement of the intercostal nerves by tumor

When pain is present in the bones or joints it is probably caused by a metastasis or it is related to hypertrophic osteo-artropathy resulting from the "toxins" circulating in the blood in this condition, also causing a "toxic arthritis," Later this will be discussed in more detail

Hypertrophic osteo-arthropathy, hippocratic fingers This symptom complex described years ago by Marie and by Bamberger, provoked considerable discussion as to whether the condition is an autonomous disease, or occurs secondarily as a complication of some other illness The question arose also whether the generalized hypertrophic bony changes and the clubbed fingers should be regarded as different stages of the same disease At the present time the consensus of opinion is that the pathologic process in the bones is secondary to some primary disease elsewhere in the body, and that this process and the simple clubbing of the fingers are identical, the latter being an earlier stage of the general involvement of the long bones The condition occurs in various inflammatory and neoplastic processes of the lungs, in diseases of the heart, of the liver and also of the lymphatic apparatus In the periost it leads to a generalized osteophytosis, in the joints, to a toxic arthritis and in the terminal phalanges to clubbed fingers The disease may be confined to one particular structure or it may attack all these structures It is probably caused by a toxic substance circulating in the blood

As we have said, it is not specific of a pulmonary neoplasm, occurring also in pulmonary tuberculosis and likewise in other inflammatory conditions of the lungs Here, then, as with the flattening of

a hemithorax, it is possible that the osteoarthropathy or its precursor, the hippocratic fingers, preceded the new growth However that may be, when this condition is present in a middle aged person a pulmonary tumor must be carefully sought Fishberg has reported that 25 per cent of his patients showed this deformity This phenomenon was also conspicuous in many of the patients of this series, and in two of them a diffuse osteoarthropathy was found The history of one patient is of particular interest and will be related here

Case 6 (B I H No 861) Onset gradual with pain and stiffness in joints and with cough Recent attacks of epilepsy Clinical diagnosis Abscess of lung, pulmonary osteoarthropathy, and epilepsy Death Necropsy disclosure of bronchiogenic cancer with cavity formation

History H M a widower, a Jew and a meat cutter, aged fifty five, who had come to America fourteen years previously, was admitted to the Beth Israel Hospital, December 6, 1928, with the complaint of pain and stiffness in the joints of his hand and feet The patient's parents died at the age of about 65 of causes unknown His wife died ten years ago Three children, brothers and sisters, were living, being in good health Except for measles at the age of 15, he had never been ill There was no history of influenza However, he had coughed for many years, producing a tenacious sputum He smoked twenty cigarettes a day and drank daily a small glass of whisky

Present illness The present illness began about two years prior to his admission with pains in the extremities and in the joints, which was diagnosed as rheumatism The condition grew steadily worse, and seven months prior to his admission, because of this illness, he was confined to bed, and remained bedridden up to the time of his entry to the hospital His cough, too, productive of mucopurulent material, was increasing in intensity Three weeks before hospitalization he coughed up blood on several occasions He developed profuse night sweats and lost his appetite He had also lost 15 pounds (6 kgm) in the last six months

Examination showed a pale, somewhat emaciated individual, with signs of a recent loss of weight He was lying quietly in bed but showed evidence of pain on slight motion His teeth were in poor condition and his tonsils were large, ragged and probably infected His appearance was most impressive, resembling somewhat that of an acromegalic His features were rather large and disproportioned and the joints looked as if there was a subluxation The lower jaw was prominent, the fingers seemed to be longer than usual showing marked clubbing with the typical watch glass nails (fig 54) Similar changes were noticed in the lower extremities (fig 55)

Examination of the heart showed no disease The blood pressure was 100 systolic and 68 diastolic

The lungs revealed a dull area occupying the entire right lower chest beginning with the angle of the scapula Elsewhere in the lungs there were scattered râles

The sputum was mucopurulent and moderate in amount It contained no tubercle bacilli The erythrocytic count totaled 4,500,000 per cubic millimeter, and the white cells numbered 10,000 per cubic millimeter, the

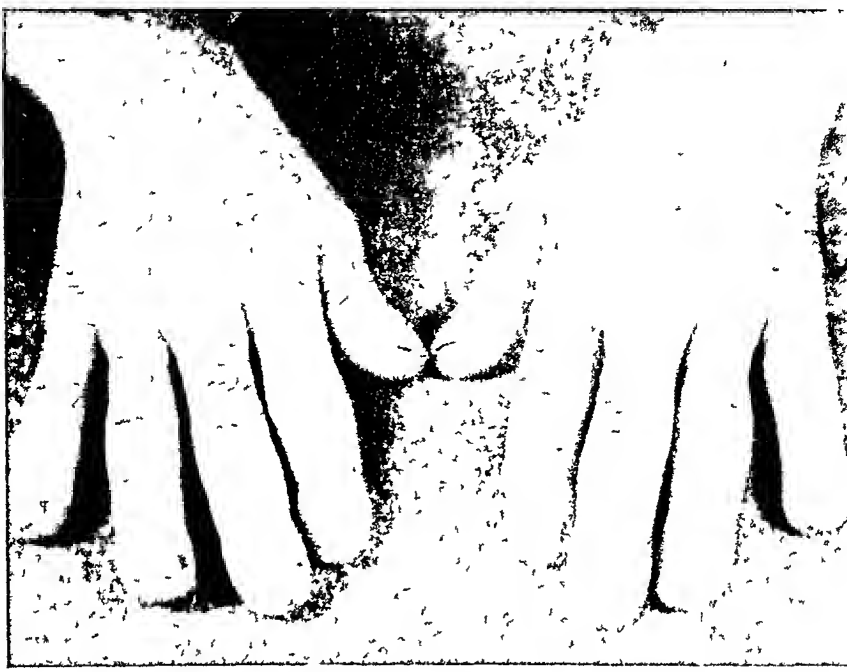

Fig 54 Case 6, Hippocratic (Clubbing) Fingers

hemoglobin averaged 70 per cent The other laboratory data were of no importance

Roentgen-ray examination of the chest showed a triangular area of mottled shadow at the mid-portion of the right lung which was suggestive of a pneumonic process The possibility of abscess of the lung could not be excluded The interlobar septum between the middle and lower lobes was considerably thickened Both sides of the diaphragm were sharply defined and the costophrenic angles were clear The left lung and the heart showed no disease

In the bones there was an extensive periosteal thickening with an irregular

FIG 55 CASE 6, CHRONIC HYPERTROPHIC OSTEOARTHROPATHY, ALSO CLUBBING OF TOES

calcium deposition, involving all the long bones, being especially marked about the phalangeal, metacarpal and metatarsal bones of both hands and both feet There was a moderate degree of atrophy of the bones of the hands and the feet (fig 55)

The soft tissues about the fingers and toes were considerably thickened, and there was clubbing of the fingers The bones of the spine and the pelvis showed slight hypertrophic changes The joints showed a slight absorption of the cartilages

The changes in the lungs were regarded as being consistent with a pneumonic process or with an abscess

The changes in the bones were interpreted as a marked degree of pulmonary osteoarthropathy

Clinical course While in the hospital the patient was seized with peculiar epileptic attacks

Under medication with salicylates, baking and massage his condition improved and he was discharged from the hospital February 1, 1929

Second admission April 21, 1929, about three months after discharge the patient was brought to the emergency ward by ambulance He was restless, irrational, tried to bite the orderlies and could not speak for fifteen minutes His legs were held in flexion, the head was retracted but not rigid he perspired profusely and tried to get out of bed

His interval history as related by a relative was as follows At home the patient was continually suffering with pains in joints, which required morphia A few days prior to his second entry to the hospital he had developed anuria and convulsions which lasted about an hour He was irrational, foaming at the mouth and irresponsive The epileptic attacks recurred, and were accompanied by loss of sphincter control

On examination he was irrational, restless, dyspneic and covered with a profuse sweat His pupils were widely dilated His thorax showed dulness to flatness over the entire right back with diminished breath sounds The left side showed ephysematous breathing and hyperresonance

Roentgen-ray reexamination of the chest showed the lower two-thirds of the right lung to be obscured by an area of dulness, uniform in character, obliterating the right border of the heart, the right side of the diaphragm and the right costophrenic angle There was no disease in the left lung

Clinical course The patient has had four typical epileptic attacks of the major type, daily During these attacks he became pale, almost death like and markedly cyanotic, he ceased breathing and his radial pulses were not palpable It was thought that he had epilepsy, either toxic or due to a cerebral abscess secondary to an abscess in the lungs

May 8, 1929 The patient died

The clinical diagnosis was Abscess of lung, pulmonary osteoarthropathy, also epilepsy

The advanced osteoarthropathy was the outstanding feature in this case Since this skeletal manifestation is secondary to some pulmonary disease, the following pathologic conditions in the lungs were considered 1 Tuberculosis This was excluded because of the fact the advanced pulmonary lesion was confined to one side, the patient's

Fig 56 Case 6, Bronchiogenic Cancer with Cavity (Abscess) Formation Confined to the Upper Lobe of the Right Lung

The gray material is degenerated neoplastic tissue The cavity communicated with a subpleural abscess The interlobar septum is very much thickened

temperature was normal and his sputum was repeatedly negative for the presence of tubercle bacilli, and finally because the roentgenologic examination, was negative for an acid fast infection 2 Syphilis of the lung, too, was dismissed because of the patient's negative venereal history, the negative laboratory and roentgenologic

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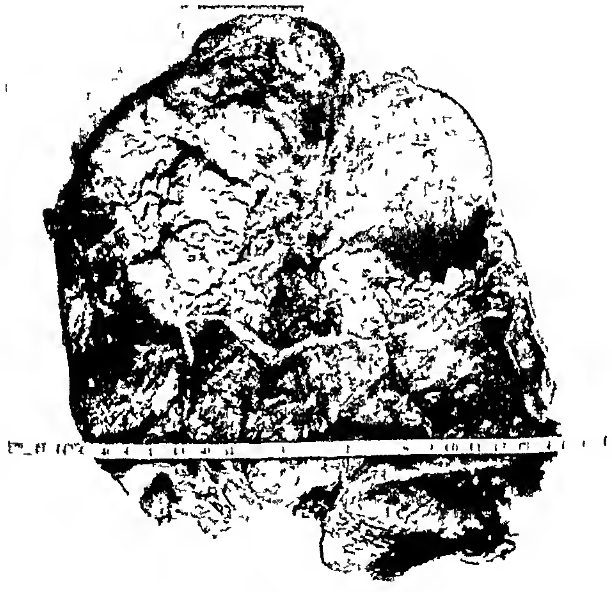

FIG 56 CASE 6 BRONCHIOGENIC CANCER WITH CAVITY (ABSCESS) FORMATION CONFINED TO THE UPPER LOBE OF THE RIGHT LUNG

The gray material is degenerated neoplastic tissue The cavity communicated with a subpleural abscess The interlobar septum is very much thickened

temperature was normal and his sputum was repeatedly negative for the presence of tubercle bacilli, and finally because the roentgenologic examination, was negative for an acid fast infection 2 Syphilis of the lung, too, was dismissed because of the patient's negative venereal history, the negative laboratory and roentgenologic

findings, and also because of the unilaterality of the disease 3 A pyogenic infection of the broncho-pulmonary tree It was believed that the process in the lung was most likely that of an abscess and of bronchiectasis The roentgenologic aspect of the diseased lung revealing "a triangular area of mottled dullness in the mid-portion of the right lung suggesting a pneumonic process" was therefore of no assistance to the clinician

At the necropsy a huge bronchiogenic cancer (right) with a large cavity in the center of the tumor, filled with necrotic malignant material, was found (fig 56)

The epileptic attcks which the patient had acquired about two months before death were possibly due to the "toxins" circulating in his blood which were also responsible for the osteoarthropathy (see above) It is remarkable that the physical signs found in the chest were so indefinite as to be of no assistance in making the diagnosis Let us consider this point in more detail

Percussion and auscultation In the chapter on the macroscopic classification of bronchiogenic cancers it was stated that as a result of the secondary changes which frequently occur in the tumor and in parts of the lungs uninvolved by the new growth, the manner of advance of the pulmonary neoplasm is inconstant Because of this the signs elicited by percussion and auscultation are often kaleidoscopic and difficult of interpretation Indeed in an instance of the diffuse lobar type the area involved by the neoplasm will be airless and evidently dull or flat However even this is not always true as the following examples will show

Example 11 The chest showed dulness and bronchial breathing from the apex to the inferior angle of the scapula, with increased voice sounds Below to the base there was flatness and a complete absence of breath sounds

At necropsy, the lung was found to be sclerosed and contracted occupying only the upper half of the pleural cavity It was diffusely infiltrated with tumor The inferior half of the pleural cavity contained hemorrhagic fluid

Example 12 The expansion of the left hemithorax was diminished Vocal fremitus on this side was diminished anteriorly and was absent posteriorly On percussion of this side, the note was flat from the apex to the angle of the scapula and dull down to the lower border of the lung as far

as the posterior axillary line Anteriorly, it was dull at the apex up to the second interspace, below that, it was normal for an interspace and then was markedly tympanitic down to the base along the axillae, as if there were air beneath the pleural cavity

On auscultation this side showed diminished bronchial breathing posteriorly at the apex, down to the angle of the scapula Below that, for two or three interspaces, the breath sounds were purely bronchial and close to the ear, at the base, there was distant bronchial breathing The whispered voice corresponded anteriorly, the breath sounds were bronchial down to the third interspace, and below that to the base there was distant bronchial breathing

At necropsy tumor was found to occupy the apical part of the lung for about 3 cm The rest of the lung, with the exception of the lower segments of the lower lobe appeared to be split vertically in two equal parts the anterior emphysematous and free of tumor, the posterior representing a firm neoplastic mass

Example 13 There was dulness over the right lower lobe with increased breath sounds, normal whispered voice and decrease tactile fremitus in this area

The post-mortem examination revealed a nearly complete occlusion by tumor of the right bronchus a little below the bifurcation Anteriorly, the wall of the right bronchus was entirely replaced by the new growth The single upper lobe branch of this bronchus which could be traced was also almost entirely occluded by tumor Below, the bronchus ended abruptly in a diffuse mass of tumor The new growth which had replaced the wall of the primary bronchus, extended by direct continuity over the anterior surface of the aorta and toward the aortic arch Posteriorly the lung was atelectatic, containing a few bronchiectatic cavities The upper lobe was tough and fibrous with a few tumor nodules at the periphery

The examples cited emphasize the protean aspect of the bronchiogenic neoplasm and the amazing discrepancy existing between the ante- and the post-mortem findings

It is true that physical signs *per se* are of little value unless interpreted in the light of clinical facts However, in the cases just cited (as in many other instances) the histories of the illness were rather characteristic of a pulmonary neoplasm yet the physical signs were ambiguous The complexity of the interpretation of the physical signs in addition to the aforementioned factor is also increased by the accumulation

of fluid in the pleural cavity and the breaking down of the tumor itself

Pleurisy Pleurisy with a serous or a sanguinous effusion was not as common a finding among our patients as among those studied by other workers But in instances when it occurred it always interfered with the prompt recognition of the true nature of the disease It also was noted that a serous exudate is more frequently met with than a hemorrhagic one and that the clear fluid may almost abruptly become bloody either spontaneously or following a thoracocentesis Thus, one of our patients showed no fluid in the chest when examined in the clinic and by the roentgen rays, in April In July one liter of serous fluid was withdrawn by thoracocentesis, and two months later, at the autopsy, a hemothorax was disclosed Pleurisy with effusion was a complication of the more advanced stages of the disease and not an early accompaniment of the tumor as reported by some authors

Degeneration of tumor Indeed, the breaking down is a feature common to all bronchiogenic cancers However there occurs a peculiar type of cancer of the lung in which there develops "central" necrosis of the neoplastic tissue resulting in the formation of a cavitation In such instances the clinical picture of the malignant process is that of an abscess of the lung and the patient is referred to a surgical clinic for an operation An example of this variety of tumor was demonstrated in case 6 In the case to follow the necropsy finding of a huge cavity surrounded by tumor was unexpected, due probably to the fact that the patient remained in the clinic for such a short time

Case 7 (P B B H No 61378) A history of cough productive of blood streaked sputum of 6 months duration Recent hemoptysis Thoracic pain at intervals Death following a fulminating hemorrhage Necropsy finding of a bronchiogenic cancer with cavity formation

History A married Jew of Russian origin, sixty years old, whose past and family histories were irrelevant, entered the Surgical Service of the Peter Bent Brigham Hospital complaining of a bilateral hernia, of hemorrhoids, and of pain in the right chest At the examination signs compatible with pulmonary tuberculosis and pleurisy were found and the patient was transferred to the Medical Service

On examination he appeared to be poorly developed and nourished He gave a history of cough productive of blood stained sputum for about six

months, and of hemoptysis which had occurred a few days before admission He had lost but 9 lbs (3 5 kg) in the last two years At intervals when breathing deeply, he complained of a pain in the right chest He had a dorsal scoliosis The right side of his chest moved slightly less than the left, and both of them moved very little The expiration was prolonged on both sides with the sounds diminished in the right upper back There was dulness just outside the sternal edge to the left The apex of the heart was not felt to the left of the sternum There were heard occasional rales over the right apex with cavernous breathing, and hyperresonance just below this area could be elicited His fingers showed definite clubbing

The question was whether the findings were due to a new growth, bronchiectasis, or possibly to a pyogenic inflammatory process

Bronchoscopic examination A 7 mm bronchoscope was passed into the right main bronchus wich gradually narrowed down in its lumen to a point above which the bronchoscope could not be passed At this point there was a smooth, rounded swelling, almost occluding the bronchial lumen, apparently originating from the medial side of the bronchus From this was obtained a specimen, which on subsequent examination proved to be a carcinoma There was no bleeding at the time of the operation

Clinical course Three days following the bronchoscopic examination the patient developed a violent vomiting spell, throwing up large quantities of blood He died a few minutes after the onset of the pulmonary hemorrhage

Necropsy This revealed a bronchiogenic carcinoma of the middle and lower lobes of the left lung with extensive central necrosis of the tumor leading to cavity formation (fig 22, p 428) There were also metastasis to left kidney, chronic adhesive fibrous pleuritis, generalized arteriosclerosis, cholelithiasis, chronic cystitis and benign hypertrophy of the prostrate

This case is interesting in many ways by the presence of a large cavity within the tumor communicating with a bronchus, by the mode of the patient's death, resulting from a fulminating hemorrhage, and finally by the absence of serious pulmonary disturbances in the presence of a massive destructive cancer, for it will be remembered that more than one half of his left lung was replaced by a largely degenerated slowly growing carcinoma (fig 22), yet he was seeking medical attention for hernia and hemorrhoids and not for his pulmonary condition

Comment

From the material studied it is apparent that a reasonable classification of bronchiogenic cancer based on clinical features is as super-

fluous at the present time as that based on their gross anatomy (discussed early in this treatise) Indeed, even the "typical cases" in our arbitrary classification display such an amazing diversity that one rarely can find a group of patients with similar symptomatology Nevertheless the "typical" category of bronchiogenic cancer represents as a rule no unusual diagnostic difficulties, provided of course one keeps in mind the fact that the disease is far from being uncommon The symptomatology may be briefly recapitulated

The onset of the disease which manifests itself in most instances in persons between the ages of fifty and seventy, is as a rule insidious A grunt or a cough productive of a mucoid or a mucopurulent sputum intimately mixed or only streaked with blood is one of the first complaints Not infrequently there occurs also a small hemoptysis A sharp stabbing pain in the chest is a characteristic sign noted by all observers and is looked upon as a cardinal symptom which other diseases rarely give Loss of weight, appetite and strength, pleural effusion, dyspnea and cyanosis, occur in all likelihood in the more advanced stages of the disease Very many patients show an asymmetry of the thorax with the narrowing of the affected side, in a high percentage of them there are clubbed fingers, and sometimes a diffuse osteoarthropathy Many of the author's patients also showed a kyphosis

The physical signs found in the chests of these patients are rather scant and not characteristic This holds equally true for most chronic pathologic conditions of the lungs The interpretation of the signs is evidently based on the same laws as that of other intrathoracic diseases The difficulty in making promptly a correct diagnosis is due to the similarities existing between this disease and a number of other chronic pulmonary diseases In fact there is not a single "irrefutable" symptom or a group of symptoms which is not common to tuberculosis, to an abscess of the lungs and to a bronchiogenic cancer Indeed most observations are to the effect that the last condition is usually confounded with phthisis or with a pulmonary abscess In certain instances it may be mistaken for an aneurism of the aorta and in two of the author's cases it was interpreted as a pulmonary infarct In the differential diagnosis one must also consider Hodgkins disease (seen usually in younger individuals), forming a rounded mass confined to

the mediastinum or as diffuse pulmonary lymphogramulomatosis (Weber), a thymoma, and a teratoma of the lung (H Christian) In a few cases echinococcus cyst and actynomycosis of the lung have been observed giving symptoms and signs analogus to those found in primary carcinoma of the bronchus

Unlike the "typical" cases, the diagnosis of an atypical case is met by insurmountable difficulties Of particular interest are those cancers that have shown early metastases to the central nervous system, in which instance the metastatic cerebral lesion simulated a rapidly growing glioma causing such acute intracranial symptoms as to make an intracranial operation an emergency procedure

In the present series of 47 cases sixteen showed metastases to the brain Of this number 12 were admitted to the service of Doctor Harvey Cushing with the diagnosis of a tumor of the brain

The patients were not emaciated nor did they show a marked loss of weight, there were no noteworthy abnormal findings recorded in the examination of their thoracic organs

In 8 of the 13 patients the disease started suddenly and in 5 it began less abruptly The patients of the first category could state accurately the circumstances, the date and often the hour of the onset of the first attack In some of them the initial symptoms were those of involvement of the motor area of the brain resulting in Jacksonian attacks, hemiplegia and weakness In others it started with headaches, nausea and vomiting In one patient it was inaugurated with mental symptoms and in another a psychopathic symptom complex occurred at a later date The optic discs of twelve patients showed a bilateral papilloedema In some of these there was evidence in the new formation of tissue that the choked discs had been present for some time

The course of the illness was most rapid in each patient so that the average period from the time of the onset of symptoms until hospitalization averaged three months One patient died a week after the onset of the intracranial symptoms and two patients had been ill for five months before being hospitalized

Signs of increased intracranial pressure probably occurred early in the course of the illness in the majority of the patients In ten patients operated upon, one metastatic nodule was removed and in two instances similar nodules were again removed (from the same location) after

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Unlike the "typical" cases, the diagnosis of an atypical case is met by insurmountable difficulties Of particular interest are those cancers that have shown early metastases to the central nervous system, in which instance the metastatic cerebral lesion simulated a rapidly growing glioma causing such acute intracranial symptoms as to make an intracranial operation an emergency procedure

In the present series of 17 cases sixteen showed metastases to the brain Of this number 12 were admitted to the service of Doctor Harvey Cushing with the diagnosis of a tumor of the brain

The patients were not emaciated nor did they show a marked loss of weight, there were no noteworthy abnormal findings recorded in the examination of their thoracic organs

In 8 of the 13 patients the disease started suddenly and in 5 it began less abruptly The patients of the first category could state accurately the circumstances, the date and often the hour of the onset of the first attack In some of them the initial symptoms were those of involvement of the motor area of the brain resulting in Jacksonian attacks, hemiplegia and weakness In others it started with headaches, nausea and vomiting In one patient it was inaugurated with mental symptoms and in another a psychopathic symptom complex occurred at a later date The optic discs of twelve patients showed a bilateral papilloedema In some of these there was evidence in the new formation of tissue that the choked discs had been present for some time

The course of the illness was most rapid in each patient so that the average period from the time of the onset of symptoms until hospitalization averaged three months One patient died a week after the onset of the intracranial symptoms and two patients had been ill for five months before being hospitalized

Signs of increased intracranial pressure probably occurred early in the course of the illness in the majority of the patients In ten patients operated upon, one metastatic nodule was removed and in two instances similar nodules were again removed (from the same location) after

recurrence six months or a year later In one patient no tumor was found In this instance the very marked edema of the brain prevented a thorough exploration Five of the patients died within two weeks after the operation and at necropsy the brains of four of these showed multiple metastases

Four patients lived five and seven months, and two and seven years respectively after the cerebral operation, with complete relief from their intracranial symptoms until the final overwhelming spread of the disease followed by rapid death

With the above facts in mind it is the author's opinion that surgical intervention is indicated in such cases, even though one is conscious that the lesion is a metastasis For, in instances when the intracranial lesion was solitary, its removal with the usual ensuing decompression had led to a prolongation of the patient's life sparing much suffering caused by an expanding intracranial lesion

The most common cerebral tumor found in persons of middle or past middle age is a rapidly growing glioma, classified as a *glioblastoma multiforme* The progress of the symptoms in this glial tumor is rapid and the majority of patients show early and severe choking of the optic discs However, the average period of survival from the onset of symptoms in patients with a glioblastoma is probably longer than that of patients with a metastatic epithelial tumor, varying from several months to a little more than a year, depending upon whether or not an operative procedure had been carried out

The differential diagnosis between an intracranial metastasis and a cerebral vascular lesion likewise represents difficulties Here the progressive character of the disease with signs of a steadily increasing intracranial pressure would make the diagnosis of a tumor more plausible The same holds true in encephalitis, although some degree of papilloedema occurs likewise in patients with this disease

There has been little experience in this group with mental symptoms, only two patients simulating a psychosis But here again the advance of the illness with the occurrence of a progressing intracranial pressure favor the diagnosis of new growth

From the above it would appear that in a person of middle age with a rather abrupt onset of symptoms and signs of a more or less rapidly developing intracranial lesion, a metastasis to the brain should be

thought of, also that the lungs are the most probable seat of the primary tumor It is, moreover, realized that even in instances when the examination of the lungs yielded no definite results, the presence of a bronchiogenic tumor should be considered

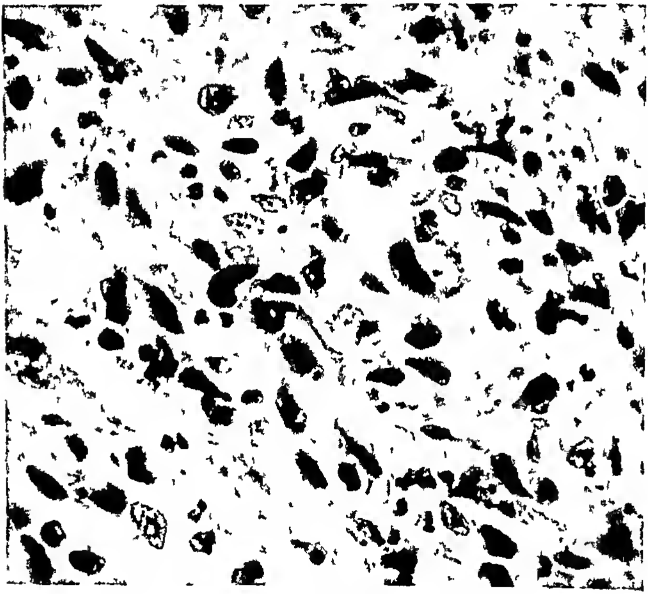

FIG 57 SHOWING THE HISTOLOGY OF A BIT OF TISSUE COUGHED UP BY A PATIENT WITH A BRONCHIOGENIC CANCER
Hematoxylin and Eosin, × 600

VIII LABORATORY METHODS OF INVESTIGATION

Expectorated material

There are no biologic tests which can be utilized as an aid in the diagnosis of a bronchiogenic cancer The complement fixation reaction (Bordet-Wassermann) is useful in that it helps to exclude syphilis of the lungs This holds equally true of the examination of

recurrence six months or a year later In one patient n
found In this instance the very marked edema of the br
a thorough exploration Five of the patients died wi
after the operation and at necropsy the brains of four
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the sputum and claimed at one time by Lenhartz and others as being pathognomonic of bronchiogenic cancer can no longer be relied upon However, in instances when the patient coughs up a bit of tissue it is important to investigate it thoroughly, for the finding of an epithelial malignant condition in such material (after it has been fixed in the

FIG 59 THE HISTOLOGIC APPEARANCE OF A HEMORRHAGIC EXUDATE FROM A CASE OF BRONCHIOGENIC CANCER

The fluid was centrifuged, and the sediment was fixed in a solution of formaldehyde ematoxylin and eosin, × 110

customary way) is conclusive evidence of the existence of a primary pulmonary neoplasm (fig 57) It will be remembered that tumors which have metastasized to the lung have never been observed to invade the bronchial wall, and hence will not yield carcinomatous material in the sputum

The pleural exudate

The presence of a serous exudate in the pleural cavity is indeed characteristic of many inflammatory conditions of the lung and pleura But when the fluid is hemorrhagic it indicates in most instances the malignant nature of the underlying process, but without telling whether it is a primary or a metastatic pulmonary lesion

The examination of the exudate for the presence of neoplastic cells is an important procedure Better results are obtained when the fluid is centrifuged and the sediment is fixed in a 10 per cent solution of formaldehyde or Zenker's fluid and run through the customary procedure of paraffin sections (figs 58 and 59) Here, too, the pathologist will not be in a position to establish definitely the original seat of the new growth But in instances where there is a question between an inflammatory and a malignant process which are believed to have originated primarily in the lung, the finding of neoplastic cells in the pleural fluid will point out the correct diagnosis

The bronchoscopic examination

The examination of the bronchopulmonary tree with the bronchoscope will indicate early a pathologic process in the bronchus, that is, a narrowing of its lumen due to the neoplastic endobronchial proliferation, or possibly to pressure from without The mucosa of the bronchus, which is the primary seat of the tumor, will show at the beginning of the disease, thickening or "roughening" of the bronchial mucous membrane In a number of instances the removal of a bit of tissue is indeed equivalent to a biopsy The importance of this procedure must, therefore, be highly recommended It is true that in instances when the tumor originated in a small bronchiole, which probably occurs in a fairly high percentage of cases, it will not be detected by the bronchoscope

Roentgen-ray examination

The purpose of this method of investigation like that of other laboratory tests is either to substantiate the diagnosis already made in the clinic, or to indicate the true nature of the pulmonary disease in doubtful cases

In bronchiogenic cancer these two requirements are fulfilled by this

procedure in a high percentage of cases A competent roentgenologist will in most instances establish whether one is dealing with a malignant or a benign process, he will often ascertain whether the process originated primarily in the lung, he likewise will define the extent of the process, and as time goes on the rate of its progress

Indeed, this method, too, is far from being infallible and much remains to be done in the way of the diagnosis of early pulmonary pathologic processes by the roentgen-rays Nevertheless, this procedure when taken alone or in conjunction with the intratracheal injection of lipiodol when added to the clinical data is apparently of the utmost value in the diagnosis of a bronchiogenic malignant disease

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fever in West Africa in the field and in the laboratory Houses for living quarters and a central laboratory, all thoroughly screened, had been erected in a suburb of Lagos, Nigeria Five of the buildings and most of the equipment had been shipped from the United States The extensive grounds had been beautified with colorful plants and red laterite drives, and there was a good tennis court Conditions were highly favorable for the work the staff included men experienced in yellow fever investigation in South America, the laboratory was well equipped, yellow fever cases were available for study, and the co-operation of government officials was excellent Up to the end of my service with the Commission the field studies were carried on by Henry Beeuwkes, Allen M Walcott, Henry Hanson, and Alexander F Mahaffy, *entomological investigations by L H Dunn, biological* studies by A S Pearse, pathological examinations by Henry R Muller, Oskar Klotz, and Adrian Stokes, and serological and bacteriological investigations by Muller, J H Bauer, Klotz, I J Kligler, Stokes, and myself At times the laboratory investigators went into the field also One engineer field assistant, B R Dyer, and two laboratory technicians, V I Glasounoff and A P Batchelder, completed the scientific staff It must not be supposed that this formidable list of professional and administrative men on the staff during a period of two years represents the actual number in Africa at any one time For example, there were only ten of us on duty at the end of 1926, including an accountant and a secretary Necessary absences on leave diminished considerably the number on duty, for the climate and general health conditions were such that eighteen months had been adopted as the maximum time for continuous service in West Africa between periods of recuperation in a temperate climate Malaria was one of the greatest risks to health, and it was considered necessary to take prophylactic quinine every day during the entire period in Africa This precaution was especially important during field expeditions and it undoubtedly kept most of us from being incapacitated by malaria from time to time

The isolation of the organism causing yellow fever had been considered an essential early step in the program of the Commission, and every effort was made during these first two years to find leptospirae or other organisms in the blood of patients, in cultures inoculated

with their blood, or in inoculated experimental animals At that time it had become generally accepted that *Leptospira icteroides* was the cause of yellow fever, for in several yellow fever epidemics in South and Central America Noguchi (3) and other experienced investigators had isolated this pathogenic organism from the blood of patients who had symptoms indistinguishable from those of yellow fever In West Africa, however, numerous blood cultures and animal inoculations failed to produce infection and only negative results were secured in many Pfeiffer tests in guinea pigs with *Leptospira icteroides* and the sera of yellow fever convalescents The constant search without positive findings became almost disheartening The leptospira was obviously not present and no other organism could be found Without some positive evidence bearing on the etiology of yellow fever, the work of the Commission would of necessity be limited largely to observations of the distribution, symptomatology and pathology of yellow fever and the study of the insect vector A new approach to the problem of finding the causative organism would be difficult to devise, for no susceptible animal was available for experimentation and the use of human volunteers was considered not to be justified by the circumstances The best hope of throwing light on the etiology lay in the remote possibility of discovering a susceptible animal, and this was impressed upon me by Dr F F Russell, Director of the International Health Division, in his parting instructions when I sailed for Africa Efforts were redoubled to find that animal, and blood from yellow fever patients was injected at one time or another into several species of African monkeys, and into guinea pigs, rabbits, white rats, white mice, native pouched rats, puppies, kittens, and goats All seemed to be insusceptible and the outlook was discouraging

In the meanwhile several towns of Gold Coast, lying inland from Accra, were becoming successively involved in sharp epidemics of yellow fever That such extensive outbreaks could occur in a native negro population was contrary to the widespread belief that nearly all the natives of West Africa, from Senegal to the Congo, have been immunized by attacks of yellow fever in childhood and that extensive outbreaks of the disease are impossible among them In this region near Accra yellow fever could not have been continuously endemic, as a large part of the adult population was obviously susceptible

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On May 15 Dr Mahaffy saw three yellow fever patients at Larteh and found mosquito larvae in 60 houses out of 62 inspected On the following day he saw four more patients The government was commencing control operations and was sending its mobile laboratory from Accra for the use of the Commission in its investigations On May 17 blood was taken for examination from four new cases by Dr Mahaffy and Dr Bauer Thus the epidemic was progressing in this native town of 3000 inhabitants, with the daily appearance of new typical cases of yellow fever, when Dr Beeuwkes and Dr Adrian Stokes reached Accra from Europe on May 25 The quarantine against Accra, on account of the yellow fever there, prevented persons who left the ship from returning to it, and Dr Beeuwkes was therefore obliged to continue his journey to Lagos without landing in Accra Dr Stokes, however, went ashore and took with him two chimpanzees purchased en route in Sierra Leone By fortunate coincidence, nine crown monkeys, purchased in Hamburg by Dr Beeuwkes, had been received from another ship on the same day and were available for inoculation

No time was lost in testing the susceptibility of the new animals, as the sharp epidemic at Larteh gave unusual opportunity for obtaining virulent blood On May 26, the day after Dr Stokes' arrival in Accra, Dr Stokes, Dr Bauer, and Dr Mahaffy visited Larteh together and bled two yellow fever patients 24 and 27 hours after the appearance of the first symptoms The rest of the story is related in detail by Stokes, Bauer, and Hudson (2) The blood was citrated, mixed, and injected into a chimpanzee, two crown monkeys (*Macacus sinicus*), and twelve guinea pigs Cultures were made also A few days later, on May 30, Larteh was again visited and blood was taken from three other yellow fever patients, 23, 30, and 55 hours after the onset of symptoms The three specimens were citrated and mixed and part of this blood was injected at once into the other chimpanzee, which had been brought to Larteh for the purpose The remainder was taken to Accra and injected into two crown monkeys and twelve guinea pigs, and cultures were made as before A third at mpt was made on June 1 Blood wa from a yellow at Larteh 30 hours after the toms, and wn monkeys and six guinea d

The results with the cultures were negative, and all the guinea pigs, and one chimpanzee remained well The other chimpanzee died of meningitis, but had no lesions like those of yellow fever The two crown monkeys first inoculated, however, developed fever, and they died eight and ten days respectively after the injection of blood At necropsy it was observed that they had pale livers, hemorrhages into the gastro intestinal tract, and other lesions suggestive of yellow fever as seen in man Three unused crown monkeys were still on hand Two were inoculated each with the blood from one of the infected crown monkeys, and the third with an emulsion of liver and kidney from one of them These three crown monkeys and the four inoculated with human blood in the second and third attempts were placed in screened crates and taken by Dr Stokes and Mr Batchelder, with due precautions, to the laboratory of the Commission at Lagos during the presumed incubation period of the disease

At Lagos the observation of the crown monkeys was continued The three which had been inoculated in Accra with material from the two fatally sick monkeys of the first group presented little evidence of value, one showed no reaction and two had fever and recovered, but one of the latter died subsequently of dysentery Of the four monkeys of the second and third groups to receive human blood, however, three had fever and died, one on the tenth day and two on the eleventh day after inoculation, while one of the second group showed no reaction The lesions, macroscopic and microscopic, of the three monkeys which died were most suggestive of yellow fever and resembled those of the two crown monkeys which had died in Accra It seemed probable that a susceptible animal had been found at last, but much experimentation remained to be done before the proof could be considered complete that the experimental disease in the monkeys was the same infection as the true yellow fever of man Unfortunately, the supply of susceptible animals had been exhausted and there was no way of keeping the infectious agent for further study Soon afterward I returned to America feeling confident that I had seen the lesions of yellow fever in monkeys at an impressive necropsy performed by Dr Stokes in the laboratory at Lagos before the Director and the local staff of the Commission

The progress of the investigation was not interrupted for long A

A Brazilian strain, the F W, was finally secured by the inoculation of a monkey with a specimen of monkey liver tissue sent us in the frozen state by Dr Aragão of the Oswaldo Cruz Institute

The cross immunity tests with these viruses were decisive, as were also supplementary tests of various sera for their protective powers against yellow fever virus, and the results obtained were published by Sawyer, Kitchen, Frobisher, and Lloyd (7) Eleven monkeys which had recovered after infection with the Brazilian F W strain all survived inoculation with the highly virulent Asibi strain from Africa and only one showed any fever To get a group of monkeys which had survived inoculation with the highly virulent African strains for testing with the American strain was more difficult, but was accomplished by including animals which had received artifically attenuated virus or had been protected against the virus by an injection of African immune serum Nine monkeys immune to African strains were tested and found to resist the F W strain from Brazil, for none of them developed fever The F W strain seldom causes death in monkeys and is therefore less satisfactory than the African strains in testing for immunity Of 24 monkeys inoculated with the Asibi strain, without artificial attenuation of the virus or injections of serum, all but one died, while of 20 similarly receiving the F W strain only two died It must not be concluded from this evidence that the African strains are characteristically more virulent than the American for man or monkey, for less virulent strains than the Asibi and the French have been obtained in Africa, and after the completion of our cross immunity experiments we received from Dr N C Davis a Brazilian strain, the S R, which rivals our African strains in virulence for rhesus monkeys

Additional evidence of the identity of the African and the American yellow fever was obtained by testing sera from persons of each region who had had yellow fever, for protective power against the virus of the other region Convalescent sera from fourteen persons who had had yellow fever in the epidemic in Rio de Janeiro were received through the courtesy of Dr Aragão and Dr Soper The diagnosis of yellow fever had been made on the basis of symptoms in each case, and in one this diagnosis had been proved by the transfer of infection to monkeys through the medium of mosquitoes These sera were

were worn The tubes were sealed in the blast lamp as soon as possible to prevent absorption of moisture Usually calcium chloride was placed in the tube above a cotton plug according to the method of J H Brown (14), but this is an extreme precaution If liver tissue was to be dried, it was ground up with sand and the resulting paste was frozen and desiccated in the same way The tubes of dried blood or liver tissue were stored in the refrigerator, although the virus in the dried state will survive for a considerable time at room temperature—just how long we do not know In using the virus, a tube was opened and the contents were mixed in a mortar with a suitable solvent, sodium citrate solution in the case of blood

The ever-mounting list of laboratory infections led us to review the technic to see if we could make it even safer, although most of the persons infected had not worked with dried virus The present standard technic in our laboratory commences with the drawing of the blood from the heart of an anesthetized monkey The blood is then defibrinated by shaking in a flask with beads, cleared of cells in the centrifuge, and immediately put into loosely-plugged test tubes, measuring about 13 by 100 mm, in amounts of 0 5 or 1 0 cc The butt of each tube is immersed in a mixture of alcohol and pieces of solid carbon dioxide and whirled until the serum is frozen in the shape of a hollow thimble in the bottom of the tube The tubes of serum are then put into the desiccator and dried under vacuum When they are taken out the next day the thimbles of pale yellow serum have shrunk and lie loose in the tubes The tubes are sealed in the blast lamp as quickly as practicable and stored in the refrigerator To open a tube, the tip is scratched with a file, flamed till sterile inside and out, and broken off A volume of distilled water equal to the original volume of serum is drawn up into the inoculating syringe and injected into the tube The dried serum dissolves in a moment and the fluid is drawn back into the syringe In this way all exposure to the virus in the dried state is avoided, and there is no need for tubing the dried material or taking it out under the glass-topped frame For convenience in securing solid carbon dioxide as needed, we have installed in the laboratory an apparatus for converting into small cakes the liquid carbon dioxide purchased in cylinders

time of publishing our results we had tested the material preserved in this way only after 154 days, but, more recently, dried specimens of blood containing the French and S R strains, and of liver containing the Asibi strain, have been found to be infective and virulent after one year of storage A specimen of the same dried liver tissue, recently retested after two years of storage, has produced yellow fever in a monkey We still have one tube of this specimen for testing on its third anniversary

Others were experimenting at the same time with methods of desiccation which did not include the preliminary freezing, and were successful in preserving the virus for considerable lengths of time, Hindle (11) for three months and Hudson and Klotz (12) for 38 days An occasional specimen prepared by simple drying in vacuum will survive longer, for a tube of dried blood prepared by Hudson and Klotz in Africa, transported to New York in a sealed tube at room temperature, and kept in the refrigerator until 155 days old, still contained enough live virus to produce yellow fever in a monkey after a prolonged incubation period

The method of preserving viruses by drying in the frozen state was described in 1911 by Harris and Shackell (13) who worked with rabies virus, and it has been used in the preservation of several viruses, including vaccine virus and Virus III, by Dr T M Rivers, who recommended it to us

Some improvements in the technic of preserving yellow fever virus have been made since our publication Originally we put 15 to 20 cc of blood, freshly drawn from the monkey's heart, into a sterile glass evaporating-dish with a covering of several layers of gauze The blood was then frozen quickly by setting the dish into a shallow pan containing alcohol and solid carbon dioxide The dish was put into an improved Hempel desiccator, previously chilled by packing in a salt and ice mixture, and dried in vacuum over sulphuric acid On the following day the dish of dried blood was taken out, and the thin, friable, porous disk was broken up and put into test tubes The tubing was done under a low glass-topped frame to prevent inhalation of the fine, light particles of blood, which might float off into the air at the mouth of the tube during the manipulations Rubber gloves

were worn The tubes were sealed in the blast lamp as soon as possible to prevent absorption of moisture Usually calcium chloride was placed in the tube above a cotton plug according to the method of J H Brown (14), but this is an extreme precaution If liver tissue was to be dried, it was ground up with sand and the resulting paste was frozen and desiccated in the same way The tubes of dried blood or liver tissue were stored in the refrigerator, although the virus in the dried state will survive for a considerable time at room temperature—just how long we do not know In using the virus, a tube was opened and the contents were mixed in a mortar with a suitable solvent, sodium citrate solution in the case of blood

The ever-mounting list of laboratory infections led us to review the technic to see if we could make it even safer, although most of the persons infected had not worked with dried virus The present standard technic in our laboratory commences with the drawing of the blood from the heart of an anesthetized monkey The blood is then defibrinated by shaking in a flask with beads, cleared of cells in the centrifuge, and immediately put into loosely-plugged test tubes, measuring about 13 by 100 mm, in amounts of 0 5 or 1 0 cc The butt of each tube is immersed in a mixture of alcohol and pieces of solid carbon dioxide and whirled until the serum is frozen in the shape of a hollow thimble in the bottom of the tube The tubes of serum are then put into the desiccator and dried under vacuum When they are taken out the next day the thimbles of pale yellow serum have shrunk and lie loose in the tubes The tubes are sealed in the blast lamp as quickly as practicable and stored in the refrigerator To open a tube, the tip is scratched with a file, flamed till sterile inside and out, and broken off A volume of distilled water equal to the original volume of serum is drawn up into the inoculating syringe and injected into the tube The dried serum dissolves in a moment and the fluid is drawn back into the syringe In this way all exposure to the virus in the dried state is avoided, and there is no need for tubing the dried material or taking it out under the glass-topped frame For convenience in securing solid carbon dioxide as needed, we have installed in the laboratory an apparatus for converting into small cakes the liquid carbon dioxide purchased in cylinders

THE PROPERTIES OF YELLOW FEVER VIRUS

The collection of strains of yellow fever virus and of blood specimens from patients for our investigations made available an abundance of material for the study of the properties of yellow fever virus Such a study was undertaken by Dr Martin Frobisher, Jr (15). He made many cultures in a wide variety of media, but was unable to cultivate any organism which might be the cause of yellow fever from the blood or liver tissue of monkeys sick with yellow fever or dead from it, or from 30 specimens of citrated blood from yellow fever patients in Rio de Janeiro. Neither could he show in guinea pigs inoculated with blood containing yellow fever virus any subsequent increase of resistance to *Leptospira icteroides*. A growing culture of *Bacillus cereus* would not adsorb the virus and keep it alive The resistance of the virus, as found in monkey serum, to several disinfectants and to heat was determined and published It did not prove possible to find a specific precipitin reaction between immune sera and various yellow fever antigens, and all attempts failed to secure a non-specific diagnostic agglutination test analogous to the Weil-Felix reaction in typhus fever. Numerous attempts to secure a skin reaction by the intracutaneous injection of live or killed virus into immune or normal monkeys were without avail Complement fixation tests, however, gave results of promise as has been announced by Frobisher (16), and his subsequent experience in Brazil has given encouragement to the belief that this test will become of value as a test of yellow fever immunity when its limitations are better understood The evidence secured through this series of studies by Frobisher supports the opinion that yellow fever is due to a filtrable virus and that bacteria and leptospirae play no rôle in its etiology.

INTRANUCLEAR INCLUSIONS

Additional evidence favoring the classification of the agent responsible for yellow fever among the filtrable viruses was announced by Torres (17), of the Oswaldo Cruz Institute in Rio de Janeiro He found and described intranuclear inclusions in liver cells in experimental yellow fever and pointed out their resemblance to the inclusions found in certain other diseases caused by filtrable viruses These inclusions were later exhaustively studied in the yellow fever labora-

tory in New York by Cowdry and Kitchen (18), who described them in detail, tracing their development in the course of the disease and comparing them with the inclusions in other virus diseases They found the inclusions in preparations of liver tissue from 10 of 39 persons who had died of yellow fever

YELLOW FEVER VIRUS IN THE MOSQUITO

What happens to yellow fever virus during its "incubation period" in the body of the vector, *Aedes aegypti?* Does it increase in the mosquito, or does it simply migrate or diffuse through the body of the insect until the salivary glands are reached and the bites become infective? If it increases in amount, does it pass through some cycle of changes in form or size? These questions have not all been answered yet When Stokes, Bauer, and Hudson (2) made the interesting observation that yellow fever virus in infective mosquitoes ground up in physiological sodium chloride solution, would not pass Berkefeld filters V and N, although the virus in monkey serum would do so, the observation suggested that the virus had larger dimensions in the mosquito than in the monkey Before accepting this conclusion, Frobisher and I (19) wished to find out if the same result would be obtained if the mosquitoes were ground up in normal monkey serum A comparison of the filtrability of the virus in mosquitoes with that in monkey serum could then be made eliminating the factors of physical differences in the suspending fluids When mosquitoes, either infective or in the incubation period of the virus, were ground up in a 50 per cent solution of the serum of a normal monkey, the virus passed freely through a Berkefeld N filter and produced yellow fever in monkeys inoculated with the filtrates When the mosquitoes were ground up in physiological sodium chloride solution and the suspension was filtered through the coarser Berkefeld V filter, the filtrate did not infect or immunize the monkey inoculated A small portion of the unfiltered suspension in sodium chloride solution, containing the equivalent of one mosquito, was injected into a monkey in a control test, and much to our surprise, this animal also remained well and was later shown to be susceptible to yellow fever virus Two other filtration experiments were considered failures because supposedly infective unfiltered suspensions of mosquitoes in sodium

chloride solution were non-infective when injected into monkeys On account of difficulties in keeping tropical mosquitoes under the highly artificial conditions of our insectary, it was decided to leave all work with mosquitoes to the laboratories of the Division which were situated in the tropics, and our work with mosquitoes ceased The principal question we had propounded to ourselves had been answered the virus of yellow fever as it exists in mosquitoes, both in their infective stage and during the incubation period, is capable of passing through Berkefeld N filters, and we have no evidence that the virus in mosquitoes differs from that in the blood of man or monkey

The mystery of the failures to infect monkeys with suspensions of infective mosquitoes in salt solution, filtered or unfiltered, was solved later in Lagos by Bauer and Mahaffy (20) They also experienced repeated failures to infect monkeys with suspensions of infective mosquitoes in salt solution, and showed that the salt solution itself had a decidedly deleterious effect on the virus This effect could be inhibited by the addition of 10 per cent of normal monkey serum to the solution This discovery explained not only the loss of infectivity of filtered and unfiltered suspensions of mosquitoes in salt solution, but also the seeming low virus content of samples of infective blood when titrated by inoculating monkeys with blood highly diluted with salt solution When the diluting fluid contained as much as 10 per cent of normal serum, these investigators were able to produce yellow fever in monkeys with quantities of blood much smaller than had ever before been found infective in this disease Even one ten-millionth of a cubic centimeter was at times sufficient

THE REACTIONS OF SUPPOSEDLY REFRACTORY ANIMALS TO YELLOW FEVER VIRUS

Various animals which seemed to resist yellow fever virus were studied by Frobisher and myself (21) in 1929 Less than two years earlier it had appeared that man alone was susceptible, but in the interval yellow fever had been produced in several species of *Macacus* monkeys by a number of investigators These findings had been confirmed in the Yellow Fever Laboratory in New York with respect to *M rhesus*, *M sinicus*, and *M cynomologus*, and it had also been found out there that *M nemestrinus* is susceptible As far as we knew

at the time our study was undertaken, proven yellow fever had not been produced experimentally in any animal outside the genus *Macacus*, although attempts had been made to infect many species It appeared, however, that some of the seemingly refractory animals could react against injections of yellow fever virus to the extent of producing antibodies in their blood, for Pettit, Stefanopoulo, and Frasey (22) had prepared immunizing sera in refractory monkeys and a horse

In our study we gave large intraperitoneal injections of monkey blood containing yellow fever virus to a collection of animals distantly related in the animal kindgom A few days later we made tests to see if the active virus was present in the circulating blood, and about two weeks after the inoculations the warm blooded animals were again bled to ascertain whether there were appreciable amounts of protective antibodies in their serum We found that yellow fever virus could persist for at least two days and remain active in the blood of three species of South American monkeys (*Cebus hypoleucus*, *C fatuellus*, and *C albifrons*), the ferret, the guinea pig, and the hibernating bullfrog (*Rana catesbiana*), but we were unable to recover the virus from an African green monkey (*Cercopithecus callitrichus*), the rabbit, or the hen in the few trials made The blood of all the warm-blooded animals developed protective substances against yellow fever after they had been inoculated, for their sera acquired the power to protect rhesus monkeys against death after injections of yellow fever virus In the cases of all these animals, except *Cebus hypoleucus*, tests were made which showed that such protective substances were not present in the blood of the same animals or others of the same species, when there had been no preceding injection of yellow fever virus The one species of cold-blooded animal investigated, the bullfrog, did not product protective antibodies, at least not in appreciable amounts, for the active virus could be recovered from the heart's blood two days after a second injection of virus, which was given 17 days after the first Antibodies, if present in quantity, would have protected the monkey inoculated with this blood even if the virus was still circulating

We secured no evidence which suggested that any of the animals underwent an attack of yellow fever, except that one of two *Cebus hypoleucus* and the *C fatuellus* and a few of the guinea pigs had rises

of temperature to 40°C or above, indicating the presence of definite fever. We are inclined to believe that the monkeys underwent a mild attack of yellow fever, for Davis (23) has published evidence that certain *Cebus* monkeys are mildly susceptible and may be experimentally infected Recently Bauer and Mahaffy (24) recovered yellow fever virus from the blood of several kinds of resistant African monkeys several days after inoculation. In some instances this was done through the bites of mosquitoes

As the virus was easily recovered from the blood of guinea pigs 15 hours, 4 days, and 5 days after inoculation, although not after 8 or 14 days, we tried to pass the virus through several guinea pigs in series If we could in this way raise the virulence of the virus for guinea pigs, we hoped to be able to use these animals in yellow fever experiments in the place of monkeys Only after several trials were we able to pass the virus through even two guinea pigs in succession and back into a monkey, and we concluded that the guinea pig did not give much promise of becoming useful to us in our studies Sellards (25) was able to pass yellow fever virus through three guinea pigs in series, and Kuczynski and Hohenadel (26) succeeded in doing so through six or seven

We concluded that the species of *Cebus* monkeys investigated were probably slightly susceptible to yellow fever virus and capable of showing symptoms, that the bullfrogs were wholly insusceptible and incapable of producing antibodies, but that the other animals studied were in an intermediate position The animals of this intermediate group all reacted to large injections of the virus by producing protective antibodies, but ordinarily they showed no symptoms or lesions recognizable as those of yellow fever

THE USE OF MICE IN TESTS OF IMMUNITY

The need for an experimental animal, smaller and more convenient for laboratory use than the monkey, was soon to be filled It was Theiler (27) of the Department of Tropical Medicine of the Harvard Medical School who made the important discovery that white mice are susceptible to yellow fever if inoculated intracerebrally, and that a fixed virus for mice, with shortened incubation period and heightened virulence, could be produced by repeated passage through these animals He used the French strain in his experiments

Yellow fever virus was found to produce a very different disease in mice from that which it produces in monkeys In mice the virus is neurotropic and its principal lesions are those of an encephalitis, with intranuclear inclusions in the ganglion cells No other distinctive lesions were found except sometimes altered blood in the stomach That the disease in mice was caused by the yellow fever virus was shown by the fact that the disease could be carried back into monkeys and could be prevented or delayed in mice by serum from recovered yellow fever patients if the serum was injected with the virus into the brain Protection seldom resulted if the serum was injected intraperitoneally and the virus into the brain The fixed virus for mice proved to be highly virulent for these animals, killing all those inoculated intracerebrally about five days after inoculation As the virulence for mice increased with successive passages through mice, the virulence for monkeys seemed to fall Adult mice could not ordinarily be infected by subcutaneous, intraperitoneal or intramuscular inoculation, which fact accounts for the failure of others to discover the susceptibility of the mouse

There is no knowing how many other animals may prove susceptible when studied by methods similar to those applied by Theiler, and it is possible that the list of susceptible animals will grow like the list of mosquitoes found capable of transmitting yellow fever under laboratory conditions (Philip (28)) Although we now know that other animals than man are susceptible and other mosquitoes than *Aedes aegypti* can transmit the infection, we still lack any convincing evidence that these other animals or these other mosquitoes play any appreciable part in the perpetuation and spread of yellow fever

In a second publication Theiler (29) has presented his experience with the use of mice in testing sera for protective substances against yellow fever virus He inoculated mice intracerebrally, in groups of six or more, with a mixture of equal parts of a suspension of fixed yellow fever virus and the serum to be tested In control tests the mice received normal serum and virus These control animals died, nearly all from 5 to 9 days after inoculation, and most of them on the sixth and seventh days The groups of mice used in tests of known immune sera acted in a different way Usually a few died like the control animals, a few more died from the tenth to the sixteenth days, and

several survived While there was considerable irregularity in the results, it was clear that the method permitted differentiation between immune and non-immune sera But, even when the virus was diluted to a 1 per cent suspension before being mixed with the immune sera, as a rule a considerable proportion of the animals inoculated succumbed within the period of observation The possibility of a protection test in mice had been established, but a practical method for wide application remained to be devised

As the International Health Division had urgent need for a protection test more practicable than that in monkeys for use in extensive field investigations, Dr Lloyd and I (30) undertook a study with the object of modifying the test devised by Theiler until it should be more sensitive and less irregular in its results Dr Theiler gave us his strain of virus fixed for mice, and thus saved us the time it would have taken to produce another such strain The Asibi strain has recently been adapted to mice in our laboratory by Dr Kitchen, and Dr Lloyd and I have done the same with the S R and P A L strains, but none of these strains has as yet acquired the high virulence of the French strain as adapted to mice by Theiler and passed by now successively through 110 mice

First we applied the test as used by Theiler and secured similar results It was evident that known immune sera would not protect regularly and completely against a 1 per cent, centrifuged, suspension of this potent strain of virus when the virus was placed in direct contact with the brain tissues The immune sera, however, usually protected some of the animals and delayed death in others To give the immune sera more chance to prevent the effects of the virus, we sought a method by which the virus would be brought indirectly and more slowly to the brain This was accomplished by injecting the virus into the peritoneal cavity and at the same time injecting a mild irritant into the brain to localize the virus there That some of the virus would circulate in the blood after a large intraperitoneal injection seemed probable in the light of the experiments of Frobisher and myself (21) with guinea pigs and other animals After trying many methods, we found that the intracerebral injection of 0 03 cc of a solution containing 2 per cent starch and 0 9 per cent sodium chloride and the simultaneous intraperitoneal injection of 0 2 cc of a 20 per cent un-

centrifuged suspension of virus-bearing mouse brain would result in the death of nearly all the mice, and usually of all of them Death took place about two days later than if the virus had been injected directly into the brain A solution of 0 5 per cent magnesium chloride and 0 9 per cent sodium chloride worked almost as well as the starch solution and could be used in the place of it The quantity of the virus injected is important, as some of the controls receiving virus without immune serum usually survived when we were using a 10 per cent suspension of the virus In testing sera we etherize the mice lightly and inject the starch solution intracranially and then inject intraperitoneally a mixture of 0 2 cc of the virus and 0 4 cc of the serum A known immune serum usually protects completely if used in this quantity, while a non-immune serum usually permits all the mice to die The mice are used in groups of six, each group in a separate battery jar The routine observation period is 14 days We have designated this modified method as the "intraperitoneal protection test in mice" to distinguish it from the "intracerebral protection test in mice" and the protection tests in monkeys We are now hopeful that the test, as modified, will prove useful in epidemiological investigations and that a similar procedure will suffice for the titration of immune sera and also of virus in mouse brain suspensions

THE FALLEN

The second epoch of yellow fever research, like the first, has been paid for with precious lives The danger of exposure to infective mosquitoes in the laboratory or in the field has long been recognized, but the greater peril from the blood and tissues of experimental animals has only recently been fully appreciated Even extreme bacteriological precautions have failed to interrupt the long series of accidental infections in the laboratories A list of twenty-nine cases of yellow fever contracted in experimental laboratories, with five fatalities,[3] has been prepared by Berry and Kitchen (31) In most

[3] These comprise five of the six deaths from yellow fever which have occurred among the professional men engaged in the yellow fever control and research work of the International Health Division, formerly known as the International Health Board, since the beginning of active operations in 1918 The one death before the period dealt with in this lecture

cases the infection was attributed to working with infectious monkey blood or tissues, but in two instances the exposure was to yellow fever in mice, and in two others to the bites of infective mosquitoes The recent illnesses have on the whole been less severe than the early ones, and it may be that long passage through monkeys has diminished the virulence for man

Why so many persons have been infected in the absence of unusual exposure through a recognized wound or a laboratory accident has been something of a mystery In most of the laboratories rubber gloves were worn in all manipulations of infective material The extreme infectiousness of blood drawn early in the disease has been explained in part by the results of experiments by Bauer and Hudson (32) performed soon after the death of Dr Adrain Stokes They found that yellow fever virus in monkey blood could infect healthy monkeys through the unbroken skin

Adrian Stokes was the first to be taken He had obtained leave of absence from his duties under the Sir William Dunn Professorship in Pathology at Guy's Hospital Medical School to accept an invitation to take part in the investigations of the West African Yellow Fever Commission of the International Health Division His career had been one of distinction Most of us remember his work in the investigation of infectious jaundice during the World War He had been a member of the first yellow fever commission sent to West Africa by the Rockefeller Foundation His name will long be honored as the senior member of the group of investigators that discovered the susceptibility of the monkey to yellow fever He was carrying on laboratory experiments which grew out of this discovery when he was

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was that of a bacteriologist on the staff of the International Health Board who had gone into an endemic area of Mexico to obtain material for study and had collected blood from a yellow fever patient It seems probable that the infection was contracted through mosquitoes rather than through the blood of the patient, as the specimen was drawn on the last day of a fatal illness, a stage of the disease in which the blood is usually not infective This first professional man to lay down his life in the campaign of the Rockefeller Foundation against yellow fever was Howard B Cross He contracted yellow fever at Tuxtepec in Mexico and died in Vera Cruz on December 26, 1921 He held the degree of Doctor of Philosophy from Johns Hopkins University, where he had specialized in bacteriology, and he had prepared himself for laboratory research in yellow fever under the direction of Dr Noguchi He had just commenced his field investigation when taken sick A career of great promise was cut short by his death

stricken. From his bed he directed the study of his own case and he insisted that his blood be taken for injection into monkeys and that mosquitoes be fed on him for transmission experiments. He died in Lagos on September 19, 1927.

The next to go was Hideyo Noguchi. He was so eminent that there is no need for me to call to mind his outstanding accomplishments or the honors which have been heaped upon him. He was a member of The Rockefeller Institute for Medical Research and his services were lent to the International Health Division so that he might resume his field investigations of yellow fever as a member of the Yellow Fever Commission in West Africa. Just as his work there was finished and he was preparing to return to America to complete his study, he came down with yellow fever at Accra in Gold Coast. On May 21, 1928, he died.

The death of Noguchi would have been a serious blow to science under any circumstances, but coming at this particular time in his career it was most tragic. Years of his life had been spent in the search for the etiologic agent of yellow fever. He had been convinced that the cause was a leptospira which he had isolated from supposed typical yellow fever cases in a true yellow fever epidemic in Guayaquil. At the time of his pioneering investigations, no experimental animal susceptible to yellow fever virus was available to him or to his experienced clinical advisers, for none had been discovered. As far as any one knew or could then find out, the yellow fever of the Guayaquil epidemic was all one disease. Noguchi undoubtedly found the etiological factor in the cases from which he isolated leptospirae, but we now have reason to believe that these were not cases of true yellow fever, but rather of leptospiral jaundice (Weil's disease). The correction of the misinterpretation of Noguchi's important finding had to wait for much serological work and the discovery of the susceptibility of the monkey to the virus of true yellow fever. The usefulness of the rhesus monkey in yellow fever research had already been recognized when Dr. Noguchi went to Africa. Making use of this animal, he satisfied himself that yellow fever as found in Africa was due to a filtrable virus and not to a leptospira. He was working to unravel the problem of the confusion between yellow fever and leptospiral jaundice when he died, robbed by a cruel fate of the op-

portunity to correct and amplify his earlier opinions regarding the rôle of the leptospira and permanently to separate into two diseases the seeming clinical entity considered in parts of South America to be yellow fever alone His isolation of the leptospira was the essential first step in this important differentiation, which has been carried to the point of demonstration by his associates at the Rockefeller Institute

The death of William Alexander Young from yellow fever took place at Accra on May 29, 1928, eight days after Noguchi had passed away Dr Young was director of the Medical Research Institute at Accra It was he who furnished laboratory facilities to the yellow fever commission during investigations in Gold Coast and lent the mobile laboratory to the Commission When Dr Noguchi arrived in Africa, Dr Young welcomed him and gave him laboratory space for his work When Dr Noguchi became sick, Dr Young undertook to look after his uncompleted experiments Perhaps he would have escaped infection if he had not entered into this self-sacrificing co-operation with Dr Noguchi and the Commission

Dr A Maurice Wakeman is rightfully included among those who fell in yellow fever service, although his disease was not the one he was studying but rather some obscure tropical infection He was a young man who brought exceptional training and experience in biological chemistry to the work of the West African Yellow Fever Commission At Lagos he carried out important biochemical studies of experimental yellow fever He had been moderately ill and was returning home when his sickness suddenly became worse and caused his death on shipboard He died on March 2, 1929

Dr Paul A Lewis has long been well known to medical scientists He contracted yellow fever in the Yellow Fever Laboratory of the International Health Division in Bahia, Brazil, and died on June 30, 1929 He had devoted his life to scientific research, and at the time of his death he was an associate member of The Rockefeller Institute for Medical Research, connected with the department of animal pathology at Princeton He was serving temporarily with the International Health Division in yellow fever research when he became infected He brought to the work a wide experience in the investigation of virus diseases

Dr Theodore B Hayne was serving in his second tour with the West African Yellow Fever Commission when he died of yellow fever on July 11, 1930 He had recently been brought into the laboratory from the field to carry on the research with mosquitoes, as he had long been specially interested in mosquitoes as vectors of disease The death of this capable young man of charming personality and great interest in research was a heavy loss

The knowledge that we have of yellow fever has been purchased most dearly It should be fully appreciated and given wide application

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CONTENTS

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The YOUNG-DIDUSCH
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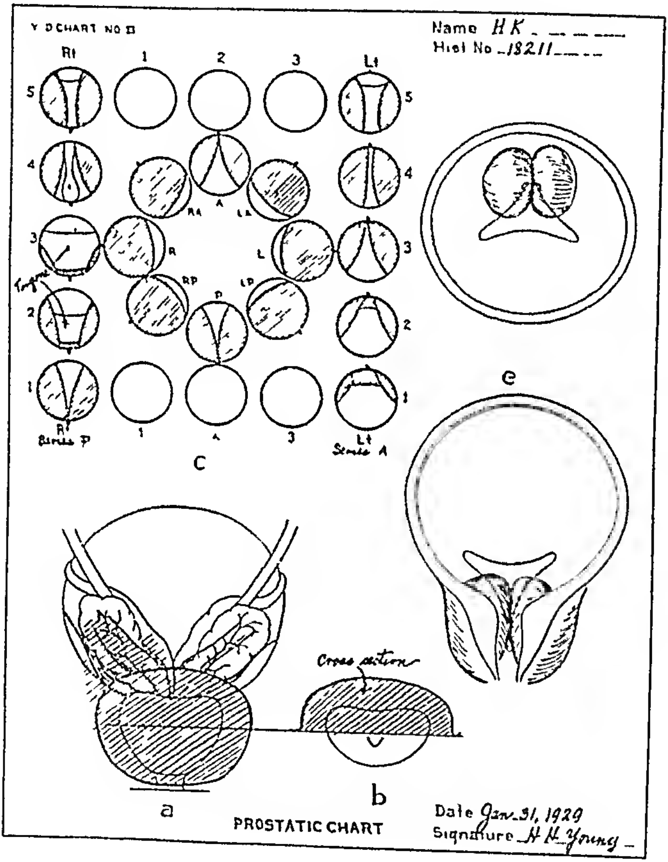
I PROSTATIC CHARTS. Five charts in one Findings on the prostate, seminal vesicles and base of bladder by rectal examination provided in *A;* the cross section in *B;* the cystoscopic study of the intravesical and intraurethral configuration of the prostate in *C; D* records interpretation of the cystoscopic findings at the vesical neck, *E,* the findings in the floor of urethra and median portion of the prostate.

(Continued on Page 7)

Illustration of the use of Chart II, overleaf

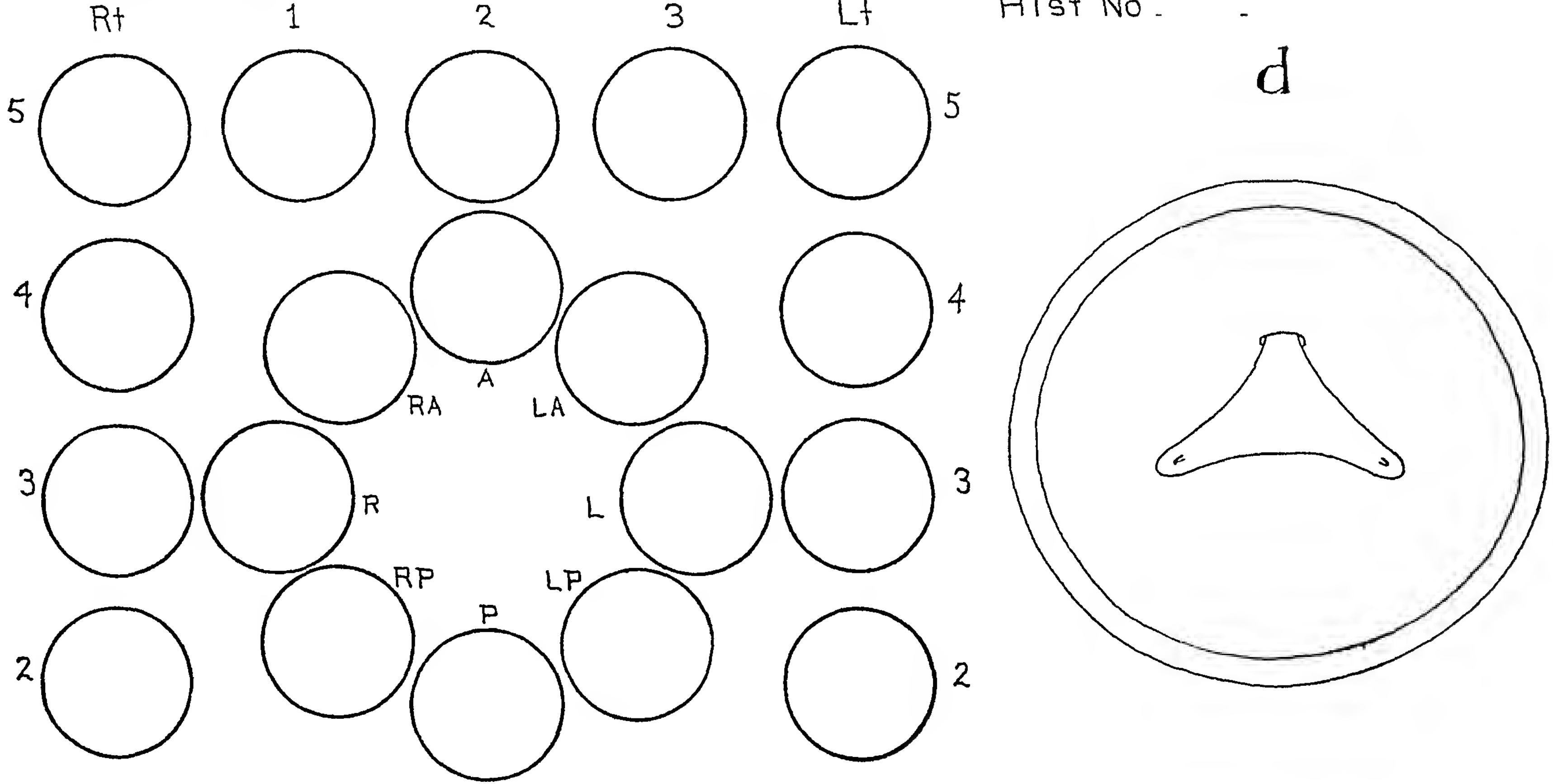


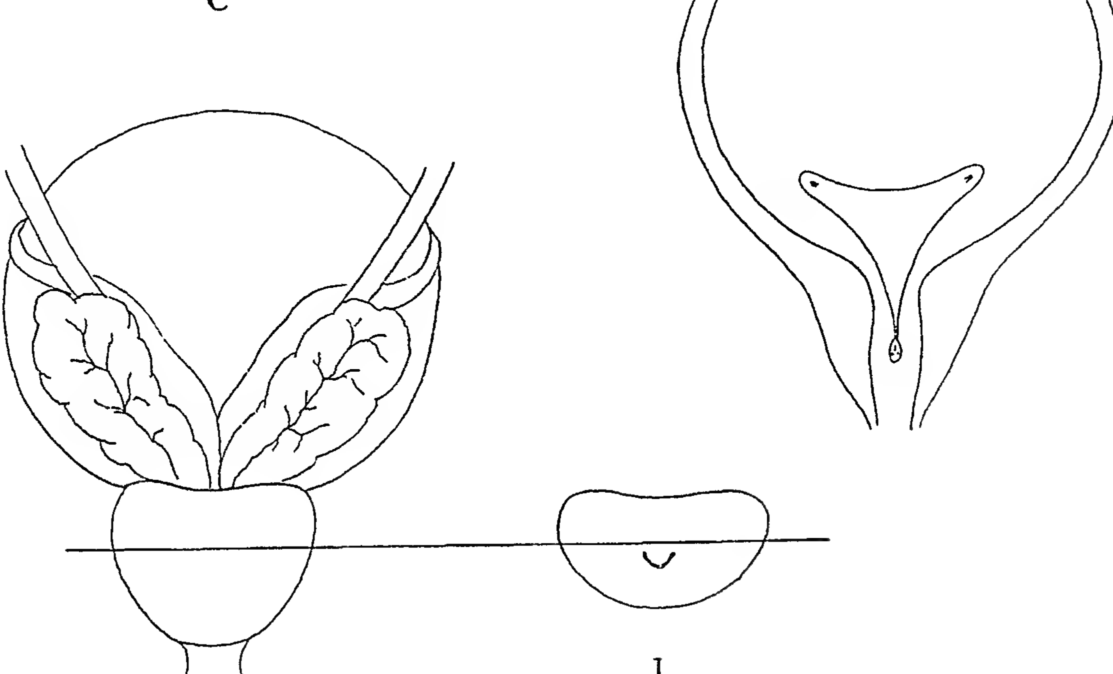
Showing use of Y and D, chart II in a case of marked prostatic hypertrophy, *a* and *b*, in which the cystoscopic views, *c*, showed marked bilateral hypertrophy, *d* and *e*, interpretations of cystoscopic findings

Y-D CHART NO.II

PROSTATIC CHART

Name.
Hist No. -





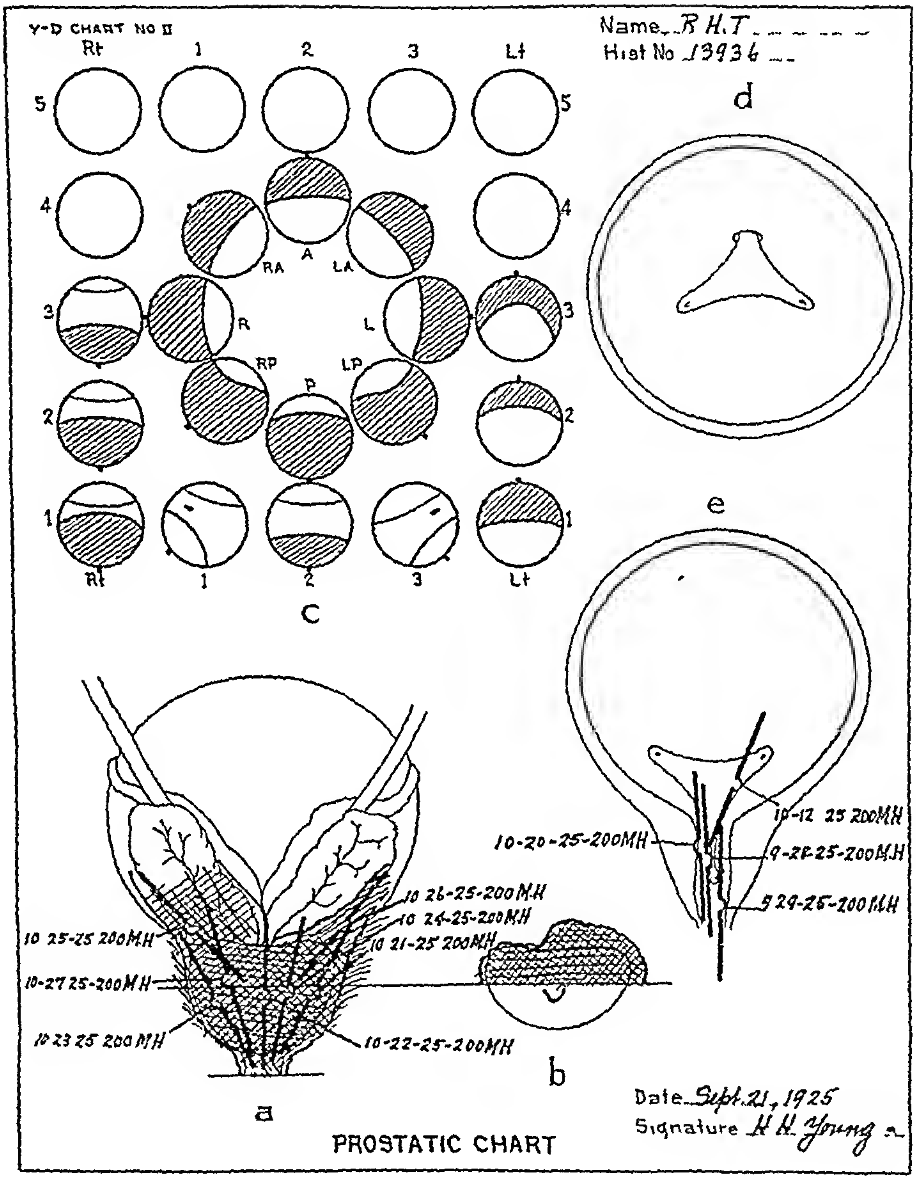
a

b

Date

Signature

Illustration of the use of Chart II, overleaf



Y and D, chart II showing findings in a case of carcinoma of the prostate, in which radium applications have been made by rectum, *a*, and by urethra, *e*. Cystoscopic findings are shown in *c*.

THE YOUNG-DIDUSCH UROLOGICAL OUTLINE CHARTS

(Continued from Page 2)

III CHART OF THE SEMINAL TRACT External diagrammatic view of testicle, epididymis and vas deferens, both right and left Posterior aspect of the prostate, membranous urethra, seminal vesicles, bladder, lower ends of ureters Cross section of the prostate

IV CHART OF THE URINARY BLADDER Six separate diagrams are provided to take care of the various aspects of the interior of the bladder

V CHART OF THE KIDNEY AND URETER Urinary passages are indicated in longitudinal section Pelvis and calices with surrounding renal cortex, ureter and their entire extent, including vesical ends and trigone, are given

VI CHART OF EXTERNAL GENITALIA, MALE, NO 1 A chart on which cases of epispadias may be recorded Front and side view and cross section are given

VII CHART OF THE EXTERNAL GENITALIA, MALE, NO 2 An additional chart on which other conditions of the genitalia may be recorded Chart presents outline of undersurface, lateral view from the left, right side of penis, dorsal aspect of penis, cross section of penis, corpora and urethra

VIII CHART OF THE LOWER GENITO-URINARY ANATOMY, MALE, RIGHT SAGITTAL A median line sagittal section through the lower urethra and genital tracts, with adjacent structures Particularly valuable for recording pathological conditions in the urinary passages, and conditions found at operation or in post-operative procedures

IX CHART OF THE LOWER GENITO-URINARY ANATOMY, MALE, LEFT SAGITTAL The same as Chart VIII, but for the left side

X CHART OF THE GENITO-URINARY ANATOMY, FEMALE, RIGHT SAGITTAL Includes the bladder and urethra, vagina, uterus, rectum, anus, and external genitalia Provides for depicting pathologic and anatomic conditions of both urinary and genital tracts, and for operations

XI CHART OF THE GENITO-URINARY ANATOMY, FEMALE, LEFT SAGITTAL Same as Chart X, but for left side

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THE VELOCITY OF BLOOD FLOW IN HEALTH AND DISEASE

The Velocity of Blood Flow in Man and Its Relation to Other Measurements of the Circulation

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CONTENTS

I INTRODUCTION AND HISTORICAL RÉSUMÉ OF THE PROBLEM OF THE VELOCITY OF BLOOD FLOW

An adequate flow of blood to the tissues implies two things In the first place, an adequate amount of blood must be expelled from the heart per unit of time In the second place, this blood must be trans-

lumination the time at which the dye appeared in the common carotid artery He studied the circulation times over many pathways in various animals and also studied the circulation times of individual organs In dogs he found that the circulation time from the right ventricle to the aorta varied from 1.7 to 8 0 seconds, according to the size of the dogs used

In 1922 E Koch (76) presented measurements of the circulation time in man in both normal and pathological states He injected 1 cc of a 1 6 per cent solution of fluorescein into the cubital vein of one arm and then obtained samples of blood at five-second intervals from the cubital vein of the other arm The dye, therefore, traversed the veins to the right ventricle, the pulmonary circulation, the left chambers of the heart, the aorta, the arteries of the arm, the peripheral capillaries of the arm and then finally the vein from which the blood was collected In 51 normal male subjects between the ages of fifteen and seventy-nine he found that the average circulation time was 20 4 seconds It should be noted that withdrawal of blood for these purposes is feasible only from the cubital vein and that in order to determine the time of arrival of such a dyestuff, a constant stream of blood must flow from the arm through the needle to the collecting tubes The formation of clots, the inaccessibility of the veins, the alteration of flow by the introduction of the needle into the vein, and the frequent difficulty of recognizing the first trace of fluorescein, all necessarily interfere with the trustworthiness of such a method (8)

Meldolesi (98) in 1925 and Koch (77) in 1928 inserted an electrode through the skin next to the radial artery or into the cubital vein Concentrated salt solution was then injected and its time of arrival was registered by means of a galvanometer connected to the electrodes

In 1927 Blumgart and Yens (7), working at the Thorndike Memorial Laboratory of the Boston City Hospital, elaborated a method according to which radium C, the active deposit of radium, was injected into the antecubital vein and the time of arrival in the other arm was determined by means of a suitable detecting device They summarized the status of the problem at that time as follows (7)

"Theoretically the most desirable measurement of the velocity of blood flow consists in establishing the separate velocities of each minute portion

of the blood along the many separate paths When one considers that the innumerable vessels in the body are constantly changing in size and elasticity, and that the blood is a suspension of corpuscles in a fluid medium, the impossibility of fulfilling the ideal requirements becomes obvious The problem is further complicated, any mean velocity measurements which depend on the insertion of a mechanical device into the blood stream defeats its ends and can, therefore, not be considered for clinical application The most feasible method appears to be the injection of some substance at one point in the body, and the measurement of the time of its arrival at another point Consideration of the problem shows that the substance to be used must fulfill the following requirements

"1 The substance must not be toxic in the amounts utilized Toxicity is of course a relative quality, for any substance, if given in sufficiently large amounts, may bring about grave consequences

"2 The substance should not be present previously in the body Estimation of additional amounts of substances already within the body is always subject to error Weber's law, moreover, is applicable According to this law, the increase of stimulus necessary to produce an appreciable increase in sensation must always bear the same ratio to the whole stimulus If, accordingly, a substance were already present, greater amounts of that substance must be injected to produce appreciable changes at the point of detection

"3 The substance must not in any way disturb the very phenomena under investigation Toxicity would introduce such an error The introduction of hypertonic salt solution would also cause an error for it would alter the blood volume, vary the speed of blood flow, and thereby modify the very phenomenon under investigation

"4 It is desirable that the substance disappear from the body with sufficient rapidity to allow of repeated measurements

"5 The substance must be readily detectable in minute amounts Were this impossible, varying dilutions of the substance would be all the more likely to produce correspondingly variable results "

Blumgart and Yens (7) found that the use of the active deposit of radium yielded a method which fulfilled the foregoing criteria and permitted clinical application in normal subjects and in a wide variety of pathological states

Blumgart and Weiss (8) in 1927 presented a critique of the method and the results of fifty-six measurements of the velocity of blood flow in fifty-three normal male individuals

The active deposit of radium was collected on a platinum needle electrode in a specially constructed chamber (12) (122) (148) (fig. 1) The needle was removed from the chamber after an appropriate length

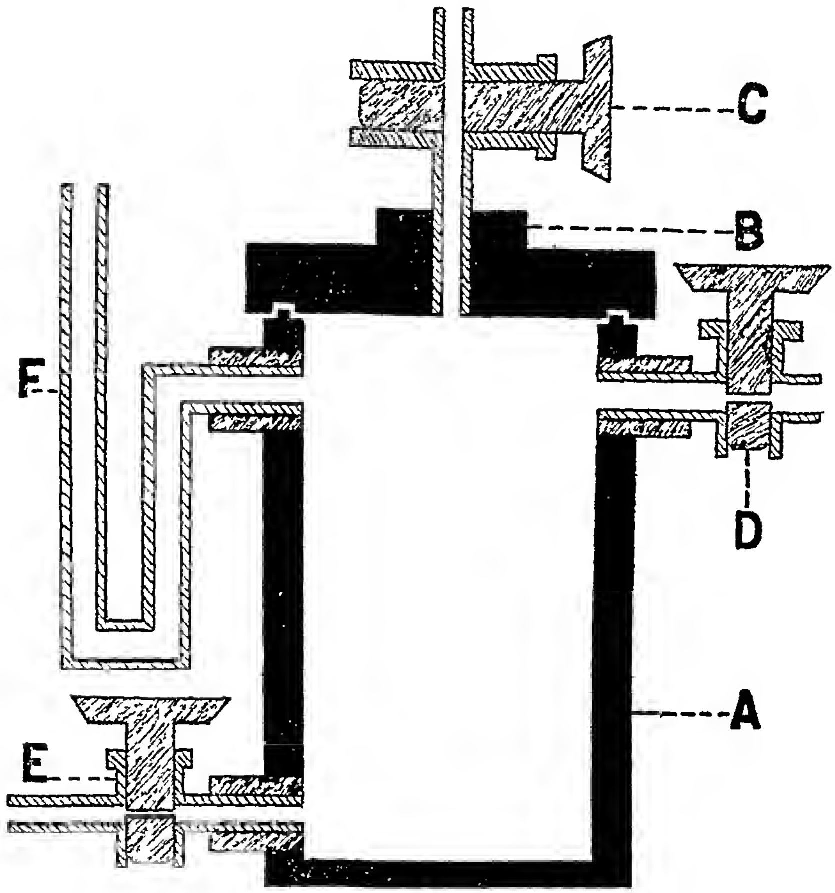


FIG 1 DIAGRAM OF EMANATION CHAMBER USED FOR THE COLLECTION OF THE ACTIVE DEPOSIT OF RADIUM

The steel chamber consists of the cylinder *A*, to which is fitted a hard rubber top plate, *B* Stopcock *C* allows introduction of the platinum electrode upon which the active deposit is collected Stopcock *E* permits introduction into or escape of mercury from the mercury The glass manometer tube, *F*, allows observation of the pressure within the chamber The radium emanation is introduced into the chamber through stopcock *D*

of time and was moistened with 10 per cent hydrochloric acid in a capillary tube Concentrated sodium hydroxid was then added until

the reaction of the fluid was neutral to phenol red The solution was then drawn up into a 1 cc tuberculin syringe, and from this injected into an arm vein The effect of an increase in volume of the blood stream could be disregarded since the volume injected ranged from 0 1 to 0 2 cc This amount of hypertonic solution is too small to exert any effect of physiological consequence

The injection was performed in the following manner A tourniquet was applied for as short a time as possible, while a sharp needle connected to a three-way stopcock was inserted into the lumen of the vein The tourniquet was then removed By connecting the needle to a glass manometer containing sodium citrate, the venous pressure was measured according to the method of Moritz and Tabora (102) The rapid descent of the small amount of citrate solution in the manometer tube and the presence of respiratory undulations indicated free communication between the needle and the vein The stopcock was then turned and the solution containing the active deposit of radium injected The volume of the solution was so small that only a fraction of a second was required for injection The duration of the injection was so small a fraction of the time which elapsed between that of injection and that of arrival at the opposite arm that it constituted a negligible error of not more than 0 5 second Three to five minutes elapsed from the time the tourniquet was removed until the active deposit of radium was injected Any circulatory changes caused by the application of the tourniquet were, therefore, reduced to a minimum

To secure a suitable detecting device proved to be a formidable undertaking The usefulness of instruments for detecting minute amounts of radioactive substances depends on their ability to detect the characteristic beta and gamma radiations which are emitted from within the atom These radiations cause ionization of any gas they traverse Conversely, under suitable conditions, the onset of ionization in a gas can therefore be assumed to indicate the presence of the radiation of a member of a radioactive series (118)

The use of an electroscope as a detector was attended with great difficulties Perfectly satisfactory shielding of the electroscope from the radiations of the active deposit as it coursed through the body was impracticable Moreover, the precise instant at which the radium

active deposit arrived was extraordinarily difficult to ascertain by this device

Kovarik's modification of the Geiger counting chamber was likewise tested (78) The necessity of a source of constant high potential, the instability of the steel needle electrode, and the relatively high

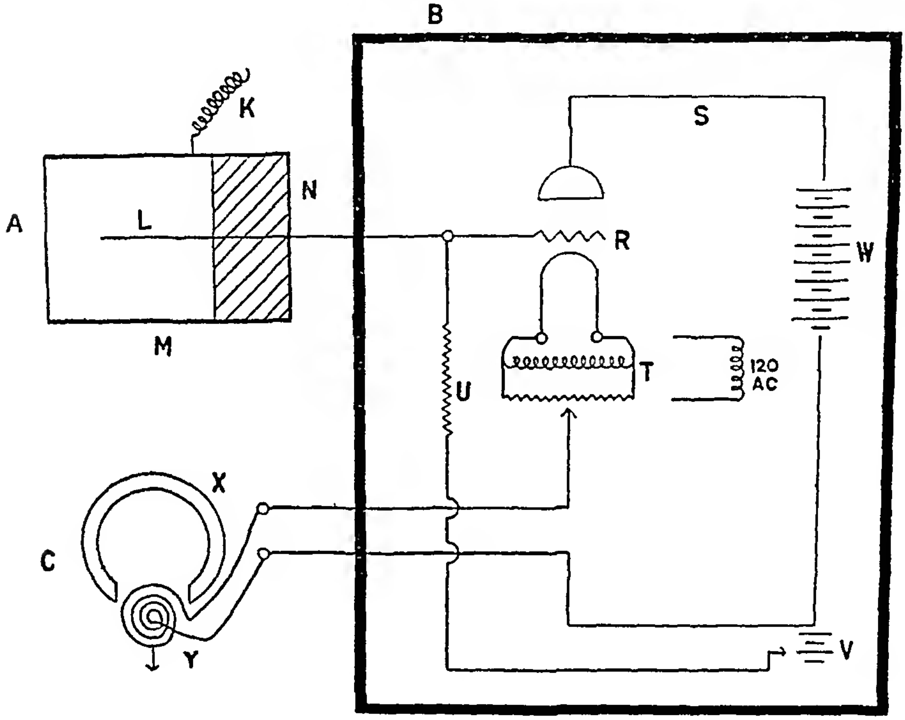


FIG 2 DIAGRAM OF DETECTOR AND RECORDING SYSTEM

M indicates brass cylinder, *A*, thin aluminum window, *K*, lead for high voltage, *N*, hard rubber plug, *L*, platinum needle, *B*, amplifying unit consisting of *R*, three electrode vacuum tube, *T*, transformer for filament of tube, *S*, plate of tube, *W*, plate batteries, *V*, batteries for bias for high grid resistance *U*, and *XYC* recording pen galvanometer

number of spontaneous discharges discouraged the choice of this mode of detection

The use of a cloud chamber of the C T. R Wilson type approached the requirements more closely While the C T R Wilson (151) cloud chamber permitted measurement of the circulation time from the antecubital vein of one arm to the antecubital artery of the other arm, the use of a Geiger counting chamber, elaborated for this special

purpose with the aid of Dr Clarence Hewlett of the General Electric Company, enabled automatic registration of the time of the arrival of the active deposit in the right chambers of the heart as well as in the antecubital arteries (13) (fig 2) The time that elapsed between the injection of the active deposit into the antecubital vein and the arrival of the active deposit in the right chambers of the heart was termed "the arm to heart time" for it was a measurement of the velocity of the venous blood of the arm to the heart The time that elapsed between the arrival of the active deposit of radium in the right chambers of the heart and in the arteries about the elbow of the arm was called "the crude pulmonary circulation time" Although the crude pulmonary circulation time includes the time of transit of

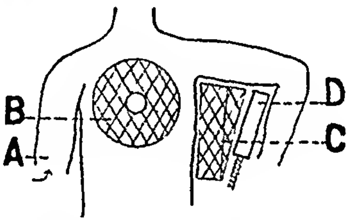


FIG 3 RELATION OF PATIENT TO DETECTORS AND LEAD SHIELDS
A indicates site of injection at antecubital vein of one arm The centrally situated hole in lead shield *B* permits insertion of detector immediately over the right auricle Detector *D* is placed behind shield *C* to ascertain time of arrival of radium active deposit in antecubital arteries

the active deposit from the left ventricle to the antecubital arteries, the velocity of arterial blood flow particularly in vessels as large as the aorta, and the subclavian and brachial arteries is conspicuously rapid and must be relatively short compared to the actual time required to traverse the lungs By applying a standard correction based on other measurements in normal individuals, the actual pulmonary circulation time of the lungs alone was estimated (13) For practical purposes, however, the crude pulmonary circulation time provides an estimate of the velocity of blood flow through the lungs

The actual relation of the patient to the apparatus is shown in figure 3

The active deposit of radium was used because of its penetrating

radiation which consists of beta particles or electrons and gamma rays which are comparable to hard roentgen rays (117, 118) These radiations can penetrate ordinary substances such as tissues or air but are absorbed by lead If, therefore, the active deposit of radium is injected into the vein of one arm at *A* (fig 3), the active deposit gives off radiations as it is carried up the arm to the right chambers of the heart. The lead shield *B*, however, prevents the radiation from reaching the detecting device which has been inserted within the centrally situated hole (13) This hole is placed immediately over the right auricle (over the sternum in the third intercostal space) so that, upon the arrival of the active deposit within that chamber, the radiations are no longer separated from the detector by lead Instead, the radiations emerge through the tissues, traverse the air, enter the detecting device and there set up a train of events which finally result in automatic registration of the time of arrival of the active deposit within the right chambers of the heart

Similarly the radiation from the active deposit as it is carried through the lungs is prevented from reaching the detector *D* by the intervening lead shield *C* Once the active deposit reaches the arterial vessels immediately in front of the detector *D*, the radiations set up a chain of events similar to that already described by which their time of arrival is automatically registered

The underlying assumptions upon which the method depended were critically examined and their validity experimentally demonstrated by Blumgart and Weiss (8) (13) The evidence for believing that the onset of the ionization effect in the detecting device accurately measured the time of arrival of the active deposit in the right auricle and the time of arrival in the large arterial vessels about the elbow was given A comparison was made of the circulation times recorded by the radium active deposit method with those obtained by testing the venous blood directly for the presence of fluorescein and for the presence of radium active deposit A comparison was also made between the circulation times of given individuals obtained by the radium active deposit method and by testing the blood from the brachial artery for the presence of fluorescein The effect of variation of dosage was also studied In brief, it may be said that direct and indirect evidence confirmed the accuracy of the method, that considerable variations of the dose of active deposit of radium did not

influence the results obtained, that the substance injected was non-toxic in the amounts utilized, that no cooperation on the part of the patient was necessary, and that measurements could be repeated after as short an interval as three hours

In 1929 the use of histamine for measuring the velocity of blood flow was presented by Weiss, Robb and Blumgart (146) Histamine phosphate in amounts of 0 001 mgm per kilogram of body weight in 1 5000 or in 1 10,000 solution was injected into the antecubital vein and the time of arrival in the small vessels of the face was observed by noting the onset of marked flushing of the face It was noted that almost simultaneously with the onset of flush a sensation was felt in the tongue of the subject and offered corroborative evidence for the observation of the color change The arm to face circulation time of the histamine method includes the circulation of the peripheral pathways as well as the pulmonary circuit, and the results obtained by this procedure are in the main roughly similar to the arm to arm circulation times gained by the use of radium C

The advantages of the histamine method over the radioactive deposit method are as follows

1 Its use is simple, requiring no complicated apparatus and technic

2 The expense of the test is minimal, and histamine is easily available

3 The test can be repeated every five to ten minutes, while the radioactive method, on account of the persistence of activity, permits repetition of measurements at three-hour intervals

The disadvantages of the method as compared with the radioactive method are as follows

1 The radioactive method is objective and more exact It makes possible the measurement of the velocity of blood flow in several areas of the body simultaneously, including important circulatory areas (pulmonary circuit), the circulation time of which cannot be measured with histamine

2 In colored and anemic people the histamine test cannot be applied

3 Patients with circulatory failure frequently become acutely dyspneic and develop other symptoms which may be alarming Ten of the group of 21 patients with circulatory failure showed such untoward reactions (146) Some patients complain of severe headache which may persist for a day

4 The test is contraindicated in patients with evidence of coronary disease (146)

II THE SIGNIFICANCE OF "CIRCULATION TIME" MEASUREMENTS

Theoretical physics of the velocity of blood flow The fundamental characteristics in a hydraulic system which determine the velocity of flow are, of course, well known The mean velocity of a stream through a rigid tube is directly proportional to its cross sectional area and the difference in pressure from point to point The product of the cross sectional area multiplied by the pressure head, when divided by the coefficient of viscosity, gives the velocity of flow This has been expressed, according to Poiseuille's Law, by the formula

$$\frac{(P_1 - P_2)\, r^2}{8\, LN}$$

where $P_1 - P_2$ is equal to the difference in pressure, r is the radius of the tube, L is the length of the tube and N is the coefficient of viscosity Formulation of the factors by such a law is valuable in so far as it serves to focus attention on the influences which determine velocity, but the futility of exact application of such a law to biological phenomena becomes apparent when one considers the constant flux of circumstances within the body The peripheral vascular bed is constantly varying, not only because of the delicate flexibility of the vasomotor arteriolar control, but also because, as Krogh and as Richards have shown, certain capillaries may temporarily be entirely or partially closed It must, moreover, be borne in mind that a certain change, such as peripheral vasodilatation, may influence the velocity of flow simultaneously in two and opposing directions The velocity of flow varies inversely as the resistance, and therefore vasodilatation, by lowering the resistance, tends to increase the velocity On the other hand, vasodilatation by increasing the cross sectional area of the flowing stream tends to decrease the velocity This, and many more continually varying relationships, serve thoroughly to confuse theoretical formulations It is by such "vasomotor breezes," as Allbutt has termed them, that application of the abstract laws of theoretical physics is confounded, for, whether one or another factor predominates, or, whether by chance they counterbalance,

cannot be prophesied For the study of the velocity of blood flow within the animal organism, direct measurements must therefore be resorted to

The meaning of the term, "circulation time" By the velocity of blood flow is meant the time required for a certain length of fluid column to pass a given point, or, conversely, how long a certain cross section of fluid takes to flow a definite distance The impossibility of securing such information along the brachial and pulmonary vessels during life is evident and so investigators, beginning with Hering (67), in 1827, have resorted to the injection of readily detectable substances and noting the time necessary for such substances to reach other parts of the vascular system The term "circulation time," as used by investigators, denotes the interval of time necessary for the fastest particle of a foreign substance to traverse the shortest available path between the point of injection and the place of detection The term "pulmonary circulation time" refers to the time necessary for a given particle to appear in the left auricle after its previous entrance into the pulmonary artery

A source of variation in the circulatory system which might lead to slight differences in the circulation time has been noted by several observers, and was first discussed by Vierordt (138) He states

> "If the first portion of the solution reaches the right auricle towards the end of diastole, it will meet blood which has flowed from the place of injection to the heart before the injection was made The next ventricular systole therefore discharges the blood containing the solution as well as the blood that has flowed just previous to the injection, and so the circulation time may be shortened by almost as much as the time required for a single systole A similar situation may arise in the left heart The error will obviously be greater when the first portion of the injection mass arrives in the auricle shortly before its next systole If this portion is small, then through dilution it will not be detectible, if, however, it is larger it will make itself manifest The more incompletely the chambers contract, and the slower the heart rate the greater will the error tend to be "

But even with the ventricular rate as low as sixty per minute this error must be less than two seconds

The path travelled by injected substances under the conditions of circu-

lation time measurements In order that changes of the circulation time should be significant, it is of primary importance that under physiological conditions the anatomical path travelled by the injected substance should be uniform That the path traversed is uniform is attested to by a considerable body of evidence Measurements of the circulation time by the radioactive method in over one hundred normal persons showed agreement within a relatively small range (8, 13) Repeated tests on the same individual at different times showed close correspondence The work of Hering (67) on horses in 1827, the investigation of Vierordt (138) in 1858 on various small animals, and, more recently, the work of G N Stewart (126, 128) on dogs and cats all strongly support the conclusion that the path traversed is a uniform one

One might contend that the circulation time is altered by changes in the number of available capillary pathways through the lungs Unfortunately, the question as to whether there is a significant vasomotor control of the pulmonary circulation is still in dispute Wiggers (149), in an excellent review of the question, concludes with Schafer that the fact that "the pulmonary system is provided with vasomotor nerves can no longer admit of doubt," but states that "provided the degree of lung inflation and heart rate remain unaltered, the vessels, that is to say, the arterioles, capillaries, and venules do not show any changes in size, nor is there any evidence of disappearance and reappearance of active capillaries"

Certain observations of G N Stewart (128) offer indirect evidence in this connection He states (page 27) "that the observed time of passage of the altered column of blood over an artery, when salt or pigment solution is infused into the, jugular vein, is in general not much longer than the time for which the infusion is kept up" This observation indicates that with animals under the experimental conditions of the study, there existed no partially closed capillaries For, if such existed, they would offer greater resistance to the blood flow than other more widely open capillaries, and the flow through them would be hindered so as to cause a tailing-out of the altered column of blood G N Stewart's observations would be in accord, however, with a situation in which the capillaries were either widely open or completely contracted Wearn, Barr and German (143),

on the other hand, by carefully cutting away the chest wall of the cat, without injuring the parietal pleura, were able to observe the capillaries of the lungs without in any way manipulating the pulmonary tissue They found that the capillaries of the lungs exhibited spontaneous variation in calibre Measurements of the velocity of blood flow by the radio-active method do not afford additional evidence, because once the time of arrival of radium C is noted, the effect remains continuously present In general, therefore, it must be stated that experimental evidence is still contradictory concerning the question of the vasomotor control of the pulmonary circulation It should be emphasized, however, that no matter how the issue may eventually be decided, the constancy of the circulation time observed by Blumgart and Weiss (8, 13) in the same persons on different days indicates that such vasomotor effects, if present, are not of sufficient importance to alter the clinical or physiological significance of the results obtained with the radio active method

The pulmonary circulation time as a measure of the mean velocity of blood flow through the lungs and its relation to the minute volume output of the heart If the vascular pathways were all equal the pulmonary circulation time would signify the interval necessary for the displacement of the blood in the lungs, and would be a measure of the mean velocity On the other hand, if there are considerable variations in the different pathways of the pulmonary circuit, or if there is a hastening on of the central stream, the pulmonary circulation time would have no necessary relation to the amount of blood displaced in the lungs, and its significance would therefore be lessened According to Tigerstedt (136) and von Kries (142), the speed of the central or axial portions of a stream may be twice that of the peripheral portions This hypothesis may seem to contain an element of plausibility, but further analysis of the theoretical and experimental evidence weighs heavily against this possibility In the first place, fluid flowing through a tube cannot be considered analogous to a piston moving in a cylinder In the case of a piston, the entire friction occurs between the piston and the cylinder, whereas in a fluid every portion of the fluid develops friction against every other portion of the fluid When one bears in mind that each smallest portion of the fluid is constantly subject to varying frictional forces, and is, therefore, undergoing

corresponding variations in its velocities, and that this situation is altered by discontinuous pulsatile waves with outward expansion and inward vibratory rebound in the case of the arteries, and by variable respiratory waves in the case of the veins, and when, furthermore, one considers the innumerable branchings, the impossibility of what is the centrally moving stream at one time remaining the centrally moving stream at all other times becomes manifest

Not only theoretical considerations, but practical experience weighs against the velocity of flow of the central stream being far greater than the velocity of flow of the outer stream If the central stream velocity were far greater than the peripheral stream velocity, one would find that, following the injection of dyes into one vein, samples of blood obtained from another vein would show considerable "stringing out," because the dye carried in the central stream would appear relatively early and would be followed only later by the dye carried in the more slowly moving peripheral stream This problem was carefully studied by G N Stewart (126, 128), who found that such "stringing out" was inconspicuous

Measurements of the velocity of blood flow by the radioactive method do not support the contention of Tigerstedt and of von Kries but, on the contrary, indicate that the pulmonary circulation time is an index of the mean pulmonary blood velocity (13, 16)

Stewart has pointed out that the mean pulmonary circulation time bears a definite relation to the quantity of blood in the lungs and the minute volume flow through the lungs (128) This relation may be expressed by the formula

$$V = Q \frac{60}{T}$$

where V is the volume output of the heart per minute in liters, Q is the quantity of blood in the lungs in cubic centimeters, and T is the *mean* pulmonary circulation time in seconds Were von Kries and Tigerstedt correct in their contention that the speed of the fastest particle as expressed by the "circulation time" is twice the mean velocity, substitution of the pulmonary circulation time for T, the mean velocity time, would result in magnifying Q, the quantity of blood in the lungs, which would then become twice too great If, on the

contrary, the pulmonary circulation time is an index of the mean velocity, the substitution should give a result which conforms to the results of animal experiments

The general average of the actual pulmonary circulation times in man by the radio active method was 6 5 seconds (13) The average of the minute volume output of the heart in normal males lying at rest is 6 38 liters (13) (55) (84) Applying the above equation $V = Q \frac{60}{T}$, $6\ 38 = Q \frac{60}{6\ 5}$ or Q, the amount of blood in the lungs, equals 589 cc Assuming that, as in animals, the total blood volume of man is about one-thirteenth of the body weight, and taking the average weight of the subjects as 70 kgm, the total blood volume would be 5 4 liters in which case 589 cc would represent 11 per cent of the total blood volume It is interesting in the light of this finding, which was the first approximation by actual measurements during life of the amount of blood in the lungs of man, to note that these results are in harmony with direct measurements made in animals (125, 79, 128) The observations in man are of importance not only because they give information in regard to the amount of blood in the lungs but also because they conform so closely to the experimental results of Kuno (79) and of Stewart (128) and indicate that the pulmonary circulation time measured by the radio-active method is an index of the mean time of blood flow through the lungs

III THE VELOCITY OF BLOOD FLOW IN NORMAL INDIVIDUALS

Koch (76) measured the time necessary for fluorescein to travel from the antecubital vein of one arm to the antecubital vein of the other arm in sixty-eight women and fifty-one men He found that the time varied from 12 to 26 seconds with an average of 20 8 seconds in women and 20 7 seconds in men Blumgart and Weiss (13) measured the time necessary for the active deposit of radium to travel from the antecubital vein of one arm to the antecubital arteries of the other arm and found that this arm to arm circulation time varied from 14 to 24 seconds in different individuals The average arm to arm circulation time in fifty-three normal subjects was 18 seconds The average arm to face circulation time measured by the histamine method in sixty-five normal individuals was 24 seconds (146) The

arm to heart time observed with the radio-active method varied from 2 to 14 seconds with an average of 6 6 seconds (13) (fig 4). The pulmonary circulation time varied from 5 to 17 seconds with an average of 10 8 seconds (fig 5) The relatively wide range of the arm to heart time reflects the great variability of the volume flow of blood in the arm as was demonstrated by G N Stewart (127) and Hewlett and Van Zwaluwenburg (69) Since measurements of the arm to heart

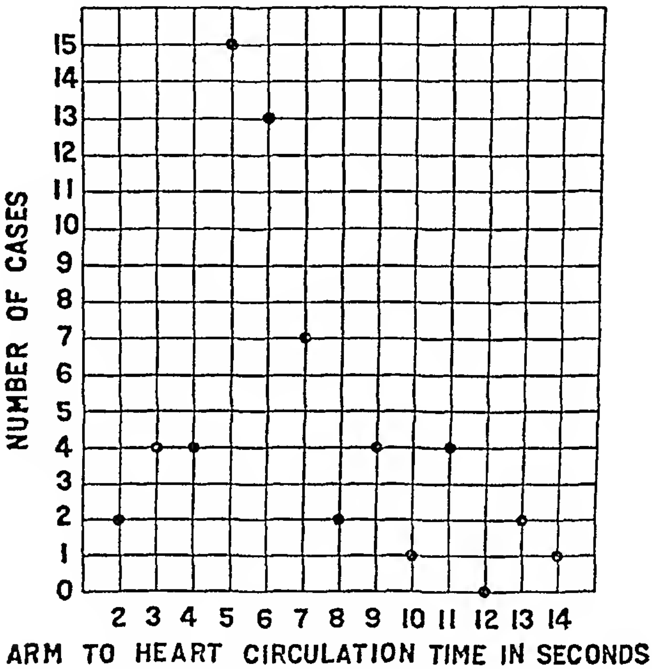


FIG 4 THE VELOCITY OF VENOUS BLOOD FROM THE ARM TO THE HEART IN SIXTY-TWO NORMAL SUBJECTS

time and the pulmonary circulation time represent data more susceptible to accurate interpretation than do estimations which include the velocity of blood flow through the peripheral vessels as well as through the lungs, future discussion of the velocity of blood flow in man will be limited to the former measurements

Duplicate measurements of the pulmonary circulation time in the same subject. In order to learn what variations may occur in a given individual, repeated measurements ot the pulmonary circulation time

were performed by Blumgart and Weiss (13) under conditions as similar as possible The maximum variation was 3 5 seconds and the average variation in eight persons was 2 seconds These results indicate that while the velocity of pulmonary blood flow may vary considerably in different subjects, it is relatively constant in a given individual

Conditions which may account for the variations in pulmonary circulation time of healthy men The pulmonary circulation time may conceivably be influenced according to the phase of respiration during

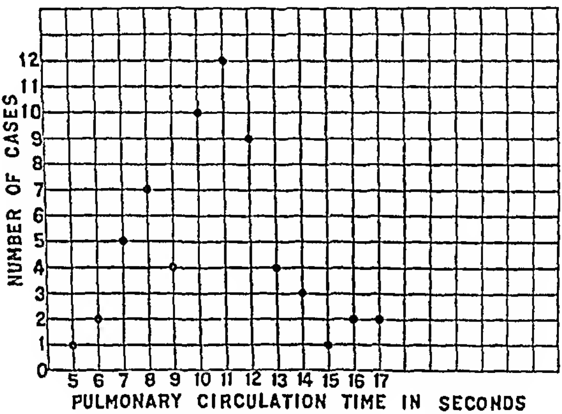


FIG 5 THE PULMONARY CIRCULATION TIME IN SIXTY TWO NORMAL SUBJECTS

which the active deposit enters the heart and pulmonary vessels (32, 33) This particular point has not been investigated although repeated measurements of the velocity of pulmonary blood flow in the same person showed that such an influence, if present, can hardly be of clinical or physiological significance This is in accord with the observations of E K Marshall (90, 91) who found that changes of 100 per cent or more in the ventilation of the lungs were not accompanied by changes in the minute volume output of the heart in trained unanesthetized dogs

The relation of systemic blood pressure to the normal pulmonary circulation time The effect, in animals, of changes of the systemic arterial blood pressure on the pulmonary circulation has been carefully studied by various observers Cloetta and Staubli (34) observed that compression of the thoracic aorta always caused increased lung volume and elevation of pulmonary arterial pressure Straub (129) found that increased peripheral arterial resistance always produced passive pulmonary congestion as indicated by increased lung volume and increased left auricular pressure Bradford and Dean (24) similarly observed that temporary compression of the aorta, or increased vasoconstriction, caused slight elevation of pulmonary arterial pressure. A rise of pressure in the pulmonary vessels would not, of course, cause

TABLE 1

Relation between arterial blood pressure and pulmonary circulation time in normal subjects

PATIENT NUMBER	BLOOD PRESSURE		PULMONARY CIRCULATION TIME	PATIENT NUMBER	BLOOD PRESSURE		PULMONARY CIRCULATION TIME
	Systolic	Diastolic			Systolic	Diastolic	
	mm Hg	*mm Hg*	*seconds*		*mm Hg*	*mm Hg*	*seconds*
255	166	94	5 5	279	98	56	3 5
286	174	84	3 0	280	78	54	6 5
250	140	70	9 5	317	92	70	4 5

an increased velocity of blood flow unless the "head on" pressure, i e, the pressure gradient, were greater In fact, a generalized increase of pressure in all these vessels, with distortion of the elastic pulmonary bed and an increase in the amount of blood in the lungs, would lead to a lengthened pulmonary circulation time It seemed of interest, therefore, to compare the pulmonary circulation times in those individuals who showed the highest and lowest arterial blood pressures (13) (table 1)

The results showed no evident relation between normal variations in pulmonary circulation time and normal variations in systemic blood pressure Back pressure effects either do not occur normally in man, or if they do occur, any increase in the amount of blood in the lungs is attended by a proportionate increase in the minute volume flow of blood

The relation between the ventricular rate of the heart and the velocity of blood flow through the lungs The average pulmonary circulation time of those individuals whose ventricular rate was above 90 per minute was 8 4 seconds, while the average of those patients whose ventricular rate was below 70 per minute was 11 2 seconds (13) (table 2) An increased ventricular rate is associated with a slightly but definitely increased velocity of pulmonary blood flow, although this relation does not obtain in each instance

The relation of the pulmonary circulation time to the venous pressure and vital capacity in normal individuals The vital capacity of the

TABLE 2

Relation between ventricular rate and pulmonary circulation time in normal subjects

VENTRICULAR RATE 90+			VENTRICULAR RATE 70−		
Patient number	Pulse	Pulmonary circulation time (crude)	Patient number	Pulse	Pulmonary circulation time (crude)
		seconds			*seconds*
256	97	11 5	250	62	13
260	94	9	253	69	10
263	102	10	266	52	13
275	105	7	280	69	10
279	94	7	285	70	13
286	98	6 5	288	68	10 5
289	92	7 5	297	62	9
310	94	7 5	320	66	11 5
313	92	12			
317	100	8			
	125	5 5			
Average	96 8	8 4		65	11 2

lungs and the venous pressure were measured at the same time as the pulmonary circulation time in all normal individuals (13) There was no correlation between normal variations in the velocity of blood flow, venous pressure, and the vital capacity of the lungs

The relation between the surface area and the velocity of blood flow The heat production and also the vital capacity of the lungs bear definite relations to the surface area in man (48) (164) These measurements express a relation between absolute quantities and surface

area The velocity of blood flow measured by the radioactive method does not refer to velocity of flow in actual units of time and distance but rather to the time necessary for the active deposit of radium to travel between certain arbitrarily chosen points If, in large persons, the distance between the two arbitrarily chosen points were proportional to the increase in surface area, and the velocity of blood flow were unchanged, a longer time would be necessary to traverse the increased distance and the pulmonary circulation time would be increased The fact that the pulmonary circulation seems to remain relatively constant regardless of the surface area of the subject indicates that the actual speed of blood flow in larger individuals is greater than in smaller persons.

The influence of age on the velocity of blood flow through the lungs The velocity of blood flow through the lungs showed no constant relation to the age of the patient, although in a few young persons in whom the ventricular rate was elevated the velocity of blood flow was somewhat increased (13)

IV THE VELOCITY OF BLOOD FLOW AND RELATED ASPECTS OF THE CIRCULATION IN THYROTOXICOSIS

Thyrotoxicosis affords an exceptional opportunity to study the effects of an increased metabolic rate on the circulation uncomplicated by many extraneous factors The importance of circulatory changes in thyrotoxicosis has always impressed students of this disease, in fact Parry (103) in 1815 originally described exophthalmic goitre as a form of heart disease He began the chapter on "Diseases of the Heart" with the following words, "There is one malady which I have in five cases seen coincident with what appeared to be enlargement of the heart, and which, so far as I know, has not been noticed, in that connection, by medical writers The malady to which I allude is enlargement of the thyroid gland "

The only available investigation of the degree to which blood flow is accelerated in thyrotoxicosis and of the relationship of such measurements to other aspects of the circulation is that of Blumgart, Gargill and Gilligan (17) They made twenty-seven measurements of the pulmonary circulation time and related aspects of the circulation in thirteen patients with thyroid disease The patients were divided into

two groups, one group consisting of nine patients without clinical evidence of circulatory insufficiency, the other consisting of four patients with definite evidence of cardiovascular disease

I Thyrotoxic patients with no clinical evidence of cardiovascular disease Twenty measurements of the velocity of pulmonary blood flow and related aspects of the circulation were made in the nine patients of this group, all of whom had exophthalmic goitre In all but one patient, observations were repeated when the basal metabolic rate had been lowered by treatment The clinical condition of the patients varied considerably Some individuals were very toxic and had experienced symptoms for many years, while in others the disease was less severe and of shorter duration Six of the nine patients were females, and three patients were males The ages of the patients ranged from 18 to 45 years

Blood In all patients the hemoglobin and red blood cell concentration in the peripheral blood were within the limits of normal

Pulse rate The pulse rates before treatment were usually elevated but became normal with lowering of the basal metabolic rate There was a general relation between the degree of elevation of the pulse rate and the increase in the basal metabolic rate In a given case, however, the relation was not always evident

Venous pressure No significant deviations from the normal were observed in the venous blood pressures before or after treatment

Vital capacity of the lungs and respiratory minute volume The vital capacity of the lungs was diminished in five of the nine patients in the absence of any evidence of circulatory failure The diminution observed was not related to the degree of elevation of the basal metabolic rate With a decrease in the basal metabolic rate toward normal the vital capacity of the lungs tended to increase although this was not apparent in every instance Before treatment when the basal metabolic rate averaged 33 per cent above normal, the average vital capacity of the lungs was 1870 cc per square meter of body surface After compound solution of iodine had been given, the average basal metabolic rate decreased to 22 per cent above normal, but the vital capacity of the lungs showed no significant change After operation, however, the average basal metabolic rate was one per cent above normal and the average vital capacity was 2010 cc per square meter of body surface

In a few patients the respiratory minute volume was measured while the basal metabolic rate was elevated and again when it had been lowered by appropriate treatment. There was some slight diminution in the respiratory minute volume with a return of the basal metabolic rate to normal, but the magnitude of the respiratory minute volume before treatment and its decrease after treatment bore no direct relation to the oxygen consumption

Velocity of blood flow The velocity of blood flow was strikingly increased, the pulmonary circulation time in some cases being the most rapid observed in any condition As in other studies (13, 14, 15), the velocity of blood flow from the arm to the heart showed considerable variation, although in most patients it was definitely increased above the normal The variability of the arm to heart circulation time was unusually great, due, probably, to the vasomotor instability of these patients The extent of the increase in the velocity of blood flow through the lungs was closely related to the extent of increase in the basal metabolic rate This relationship was present in each individual case and is also shown by the average results Blumgart and Weiss (13), in a study of fifty-eight normal persons, found the average arm to heart circulation time to be 6 6 seconds, and the average crude pulmonary circulation time to be 10 8 seconds Blumgart, Gargill and Gilligan (17), in the patients with thyrotoxicosis in whom the basal metabolic rate averaged 33 per cent above normal, observed an average arm to heart circulation time of 4 9 seconds and an average crude pulmonary circulation time of 5 9 seconds These results signify an increased velocity of blood flow from the arm to the heart of 34 per cent and an increased speed of blood flow through the lungs of 83 per cent above the average of normal

As the basal metabolic rate became lower, the velocity of blood flow likewise approached normal This is shown graphically in figure 6 The slowing in blood flow toward normal as the basal metabolic rate was lowered by Lugol's solution affords additional rational basis for the preoperative administration of compound solution of iodine

II Patients with thyrotoxicosis and clinical evidences of cardiovascular disease Seven measurements of the velocity of blood flow and related aspects of the circulation were made in the four patients of this group Signs or symptoms of circulatory insufficiency had been present pre-

viously but were absent at the time of the test, although one subject showed auricular fibrillation at the time of the first, but not at the time of the second series of measurements The vital capacity of the lungs was lowered in all patients, while the venous pressure was within the upper limits of normal The velocity of blood flow through the lungs, although conspicuously increased, was slightly slower than the average

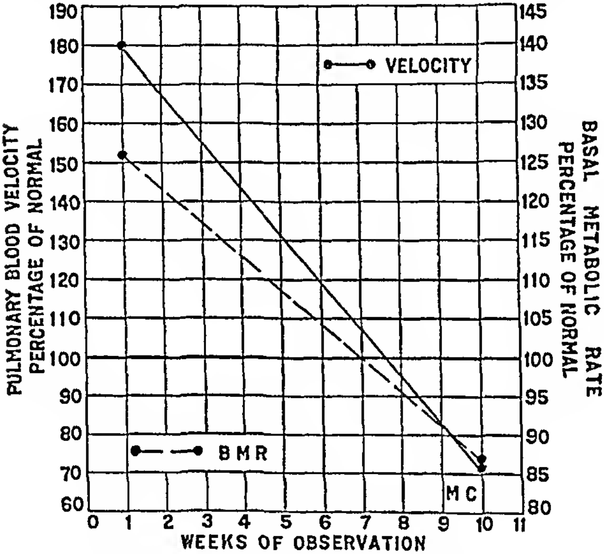


Fig 6 Relation of the Velocity of Blood Flow through the Lungs and Basal Metabolic Rate in Patient M C

Subtotal thyroidectomy was performed during the fourth week of observation

velocity observed in the group of patients without cardiovascular disease but with similar basal metabolic rates The pulse rate was generally increased in proportion to the elevation in the basal metabolic rate as in the preceding group of patients

General discussion of measurements in thyrotoxicosis The work done by the heart consists mainly in expelling the blood into the aorta and

into the pulmonary artery against the existing pressures, and in imparting to the blood a certain velocity The conspicuously increased velocity of blood flow found in subjects with thyrotoxicosis emphasizes the strain under which the heart labors in these patients even when the body is under basal metabolic conditions.

Certain facts become more significant when considered in relation to the augmented velocity of blood flow in thyrotoxicosis The hot, flushed, salmon-colored skin, the tendency to perspire, the higher pulse pressure, the tendency to greater blood volume (135), and the diminution in the vital capacity of the lungs observed clinically (110) suggest that considerable vasodilatation is present and that the functional cross sectional diameter of the peripheral and pulmonary vascular bed is increased The relation between volume flow and velocity flow through tubes of known diameter is a simple one and is expressed by the equation

$$v = \frac{a}{\pi r^2}$$

where v is velocity flow expressed in seconds, a is the volume flow per second, and r is the radius of the tube If other factors remain equal, an increase in the functional cross sectional area of the vascular bed would tend to diminish the speed of blood flow The fact that the velocity of blood flow is so strikingly increased in thyrotoxicosis in spite of the existence of considerable vasodilatation is further evidence of the extreme strain under which the heart labors (52)

Although the second group of patients experienced dyspnoea on the slightest exertion, the velocity of blood flow was only slightly slower than that observed in similar patients without cardiovascular disease (group I) This fact emphasizes the close interdependence of the circulatory-respiratory-metabolic mechanism Increased tissue metabolism cannot take place unless there is a proportionate increase both in blood flow and in effective pulmonary ventilation. The observations on the velocity of blood flow in the patients of group I, in whom there was no evidence of cardiovascular disease, indicate the degree to which the velocity of blood flow was increased to satisfy the increased metabolic demands of the tissues A blood flow less rapid than this in the patients of group II was evidently inadequate and

was accompanied by dyspnoea on the slightest exertion This finding is of interest for, while the velocity of blood flow was slightly slower in the patients of group II than in the patients of group I, it was nevertheless much more rapid than that found in normal subjects *The question whether a given velocity of blood flow is adequate, therefore, cannot be decided in any absolute terms but only in relation to the metabolic rate of the particular patient According to this concept the term "normal velocity of blood flow" denotes the velocity of blood flow found in normal subjects with a normal basal metabolic rate*

The extremely rapid velocity of blood flow observed in patients with thyrotoxicosis affords additional information why such individuals experience signs and symptoms of circulatory insufficiency on but relatively slight exertion Boothby and Plummer (23) have shown that a given amount of work by thyrotoxic patients is accompanied by a disproportionate rise in the basal metabolic rate requiring a similar disproportionate rise in ventilation and in the volume flow of blood Rabinowitch (110), Lemon (80) and others have observed that the vital capacity of thyrotoxic patients is greatly diminished, thereby imposing a limitation on the degree to which the ventilation can be increased The work of Liljestrand and Stenstrom (81), Bock (22), Kininmonth (75), Burwell, Smith and Neighbors (28), Means and Newburgh (96) and others indicates that the minute volume output of the heart in thyrotoxic patients at rest corresponds to that in normal individuals doing light work This means that the "reserve" in the minute volume output of the heart is partially utilized by thyrotoxic patients even while at rest The extremely rapid velocity of blood flow found by Blumgart, Gargill and Gilligan (17) indicates similarly that what may be termed the "reserve" in the velocity of blood flow has been seriously encroached upon In brief, a thyrotoxic individual experiences dyspnoea more readily than a normal person because (*a*) an increased gaseous exchange is necessary, (*b*) a greater expenditure of energy and hence a relatively greater degree of hyperpnea is necessary to accomplish a given task, (*c*) the pulmonary bellows are much less efficient, (*d*) the "reserve" in the minute volume output of the heart has been moderately, and the "reserve" in the velocity of blood flow has been greatly encroached upon even while the patient is at rest

The greatly increased work of the heart even under basal conditions serves to explain the frequency of circulatory insufficiency in thyrotoxicosis It cannot be stated on the basis of present knowledge whether the frequency of cardiac damage in this condition is due entirely to the increased work of the heart or partly to a specific toxic effect on the heart

The increased velocity of blood flow in thyrotoxicosis, however, probably occurs to meet the demands of the elevated metabolic rate and not as a result of a toxic effect on the heart Blumgart, Gargill and Gilligan (17) have observed several patients with essential hypertension in whom the basal metabolic rate was elevated as high as plus 33 per cent without clinical evidence of thyrotoxicosis The velocity of blood flow through the lungs in these subjects was similar to that observed in thyrotoxic patients with equally high metabolic rates but without hypertension The findings are in accord with certain measurements of the minute volume output of the heart by Davies, Meakins and Sands (44) and by Liljestrand and Stenstrom (83) The increased burden imposed by the elevation of the basal metabolic rate is of serious import to the already overworked heart and indicates the advisability of employing appropriate measures to reduce the basal metabolic rate in such patients Reduction of the basal metabolic rate, while tending to lessen the amount of the cardiac work, could not be expected to affect the degree of the arterial hypertension Similar considerations probably apply to other states in which the metabolic rate is elevated, such as leukemia and fever

V THE VELOCITY OF BLOOD FLOW AND RELATED ASPECTS OF THE CIRCULATION IN MYXEDEMA

The clinical aspects of the circulation in myxedema have aroused widespread interest, but knowledge of the pathologic physiology of the blood flow in this condition is meagre In the only available study of the velocity of blood flow by Blumgart, Gargill and Gilligan (18), sixteen series of measurements were made in seven patients in order to correlate the clinical manifestations of myxedema with changes in the velocity of blood flow, basal metabolic rate, pulse rate, plasma volume, venous and arterial pressures, respiratory minute volume and vital capacity of the lungs In each patient measurements made

when the basal metabolic rate was low were compared with measurements made subsequently when the basal metabolic rate had been elevated to normal by appropriate doses of desiccated thyroid gland by mouth All subjects were women between the ages of 45 and 58 years, except one woman who was 18 years old

Blood "Secondary" anemia was observed on examination of the blood of every patient No significant change in the anemia was noted in the relatively short time that intervened between the blood flow measurements before and after thyroid treatment The occurrence of anemia in myxedematous patients and its tendency to disappear with thyroid therapy have been noted by Emery (50) and others The patients of Blumgart, Gargill and Gilligan (18) were not studied over a sufficient length of time to observe a return of the blood to normal The dilution of the blood with the increase in plasma volume which occurred following thyroid medication was sufficient to obscure any possible slight increase in the absolute number of red blood cells

The plasma volume was measured both before and after thyroid treatment by the brilliant vital red method used by Thompson (135) The results agreed in general with those of Thompson (135) who found that the plasma volume per kilogram of body weight is low in myxedema and that a significant increase occurs after administration of thyroid gland

Pulse rate and pulse pressure The pulse rate was low in the patients studied and bore a general relation to the basal metabolic rate although an exact parallelism was not present in each individual case The pulse rate averaged 65 per minute before treatment compared with an average of 93 following adequate thyroid therapy Likewise, the pulse pressure was small when the basal metabolic rate was low and tended to increase somewhat after treatment These observations are in agreement with those of Davies and Eason (43) and with those of Willius and Haines (150) who noted an average increase in the pulse pressure from 36 mm mercury before treatment to 45 mm after treatment

Venous pressure The venous pressure was within the limits of normal in all the patients, a fact which is in accord with the absence of clinical manifestations of congestive heart failure

Vital capacity of the lungs In all subjects, the vital capacity of the lungs was strikingly diminished in the absence of any signs of congestive failure and did not show a significant change following treatment No explanation of this phenomenon is available (80, 92) The extent of diminution in the vital capacity was not closely related to the degree of lowering in the basal metabolic rate

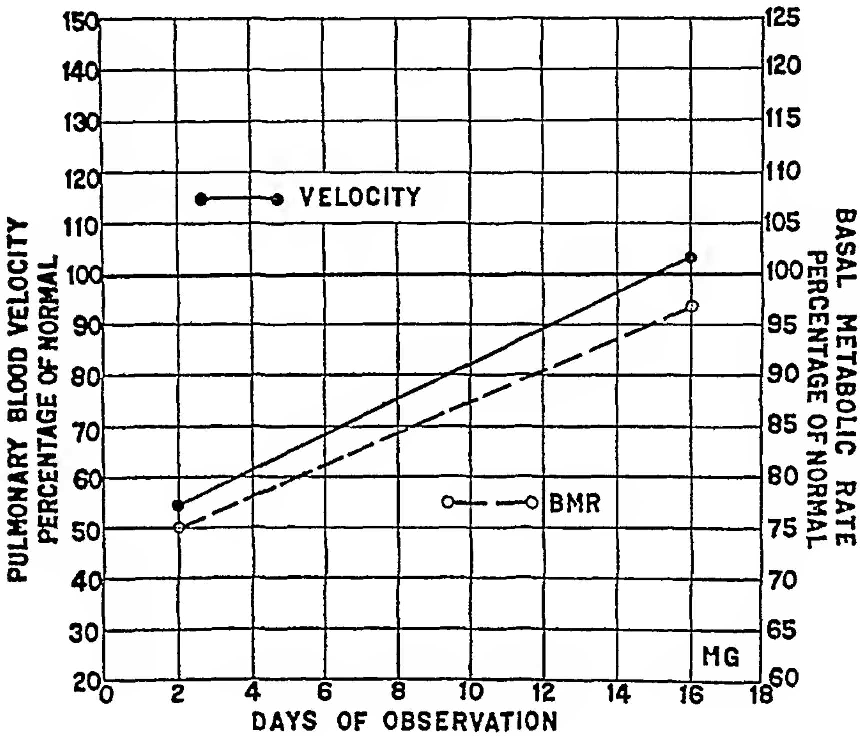


FIG 7 THE RELATION BETWEEN PERCENTAGE VARIATIONS IN THE BASAL METABOLIC RATE AND THE VELOCITY OF BLOOD FLOW THROUGH THE LUNGS IN PATIENT M G BEFORE TREATMENT AND AFTER TREATMENT

The circles (o) denote observations of the basal metabolic rate, the solid dots (●), observations of the pulmonary velocity of blood flow

Respiratory minute volume The respiratory minute volume was conspicuously decreased before treatment and always rose significantly as the basal metabolic rate increased The average respiratory minute volume per square meter of body surface before treatment was 3 2 liters compared with 4 1 liters after treatment

Velocity of blood flow The velocity of blood flow was strikingly slow in each of the seven patients with myxedema This was evident in both the arm to heart blood flow (the arm to heart circulation time) and the blood flow through the lungs (the pulmonary circulation time) The arm to heart circulation time showed considerable varia-

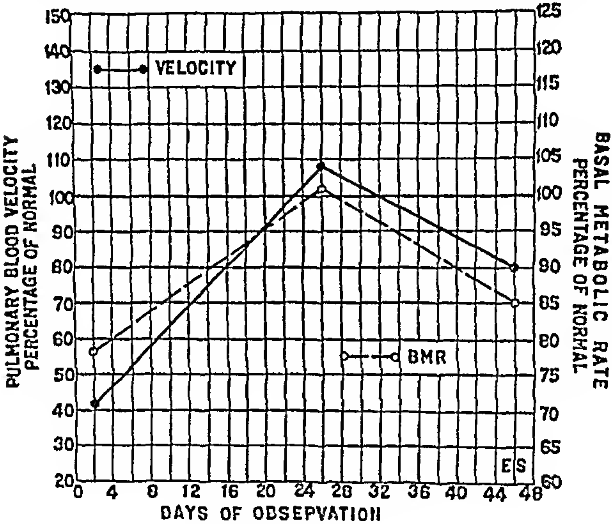


FIG 8 THE RELATION BETWEEN PERCENTAGE VARIATIONS IN THE BASAL METABOLIC RATE AND THE VELOCITY OF BLOOD FLOW THROUGH THE LUNGS IN PATIENT E S

Desiccated thyroid gland was given during the first 24 days of observation The third pair of observations was made after thyroid medication had been discontinued The circles denote observations of the basal metabolic rate, the solid dots, observations of the velocity of blood flow through the lungs

tion because of the relatively great spontaneous fluctuations in the arm blood flow (13, 14, 15) The degree of slowing in the blood flow through the lungs corresponded closely with the degree to which the metabolic rate was lowered After adequate desiccated thyroid by mouth, the rise in the metabolic rate and the increase in the velocity

of blood flow to normal took place simultaneously and closely paralleled each other (figs 7 and 8)

The slowing of blood flow in myxedema was not entirely unexpected but the degree of slowing was striking, being almost as great as that observed in patients with rheumatic valvular heart disease and auricular fibrillation, who had previously suffered from severe circulatory decompensation and showed symptoms or signs of congestive failure at the time of the test (14) The absence of evidence of circulatory insufficiency in the myxedematous patients with a speed of blood flow approximately the same as that of these patients with heart disease again emphasizes the fact that the question of whether a given speed of blood flow is adequate can be decided only in relation to the metabolic needs of the tissues (17)

None of the myxedematous patients showed evidence of cardiovascular disease Zondek (154), Assman (1), Fahr (54) and others have described a form of myocardial failure characteristic of myxedema which is alleviated only by thyroid therapy On the other hand, Means, White and Krantz (97) in a study of forty-eight patients with myxedema encountered but one such case Willius and Haines (150) in 162 cases found no evidence of heart failure or organic cardiovascular disease that could be attributed to the myxedema, and Christian (29) similarly stated he had never observed the condition

More numerous examples of the opposite course of events are available, namely, thyroid therapy precipitating circulatory insufficiency rather than alleviating it Swan (133) has reported a patient with myxedema in whom fibrillation of the auricles appeared whenever thyroid substance was administered, the heart action returning to normal whenever the drug was discontinued. Read (113), and Means, White and Krantz (97) have reported cases in which the administration of thyroid substance caused attacks of angina pectoris, and Sturgis and Whiting (132), and Pratt and Morton (109) observed patients in whom, at each attempt to give thyroid gland, the signs of congestive failure appeared Christian (30) has laid particular emphasis on the danger of increasing the heart action of certain myxedematous patients by thyroid medication

The measurements of the velocity of blood flow in patients with myxedema offer a rational explanation for the development of clinical

manifestations of myocardial insufficiency following thyroid therapy The great increase in blood velocity that occurs when the metabolic rate is raised to normal necessitates a conspicuously increased amount of work by the heart Because of this and because the metabolic needs of the myocardium have risen along with those of the rest of the body, the blood supply to the heart must be increased With the frequent occurrence of hypertension and arteriosclerotic narrowing of the coronary vessels noted by Fishberg (58) and others in cases of

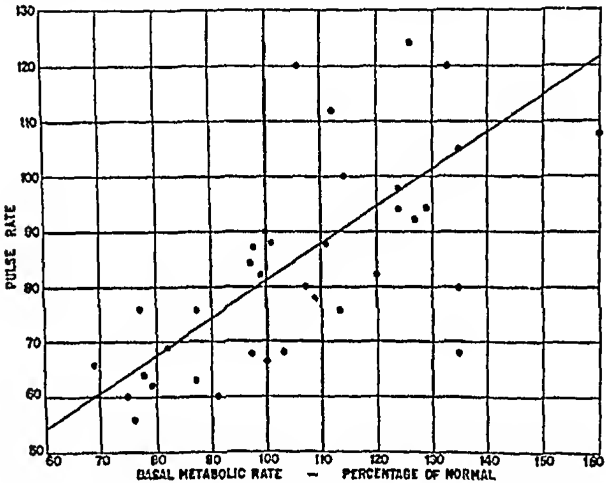


FIG 9 THE RELATION BETWEEN THE PULSE RATE AND THE BASAL METABOLIC RATE IN PATIENTS WITH MYXEDEMA AND THYROTOXICOSIS

myxedema, the necessity for cautious administration of thyroid substance and the frequent advisability of previous digitalization is apparent

VI COMPARISON OF CHANGES IN THE PULSE RATE, IN THE BASAL METABOLIC RATE, AND IN VELOCITY OF BLOOD FLOW IN MYXEDEMA AND THYROTOXICOSIS

In figures 9, 10 and 11 each dot represents an observation on a patient with thyrotoxicosis or myxedema either before or after treat-

ment The results that approach normal values represent findings in thyrotoxic patients after thyroidectomy or in myxedematous patients after thyroid substance had been administered (17, 18)

The relation between the basal metabolic rate and the pulse rate Figure 9 shows the relation between the pulse rate and the basal metabolic rate in patients with myxedema or thyrotoxicosis both before and after treatment While a general correlation is apparent, the varia-

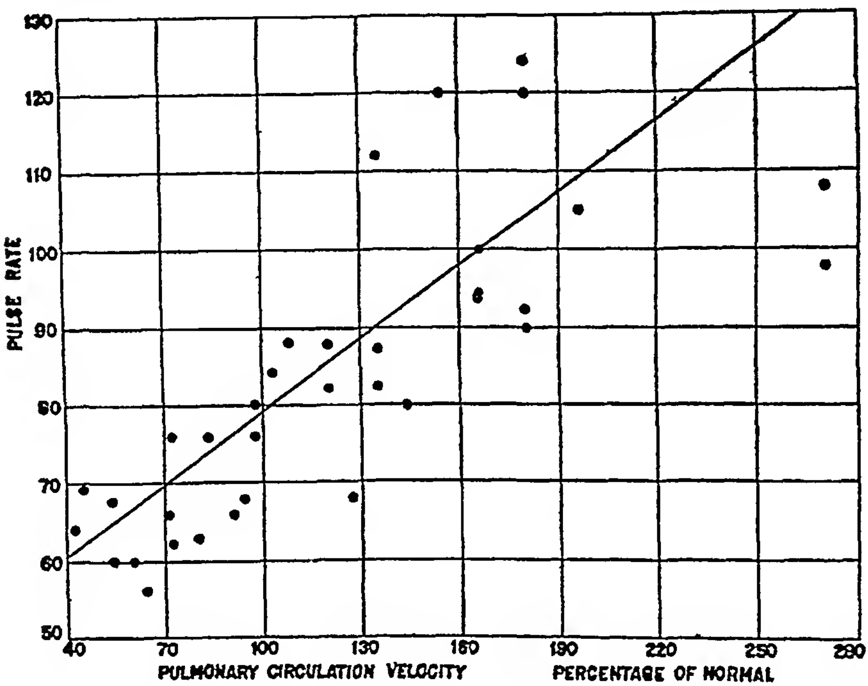


Fig 10 The Relation between the Pulse Rate and Percentage Variations in the Velocity of Blood Flow through the Lungs in Patients with Myxedema and Thyrotoxicosis

tions of individual measurements are considerable A similar relationship between the basal metabolic rate and the pulse rate has been noted by Sturgis and Tompkins (131) and others (112) in patients with thyrotoxicosis and by Minot and Means (99) in patients with chronic leukemia The observed variations are probably due to the fact that in order to increase the minute volume output of the heart to meet increased metabolic demands, both the stroke volume and the number of beats per minute are increased but in varying proportion

in different patients Similar variations in response can be observed in normal persons performing a standard exercise test (5)

The relation between the pulse rate and the velocity of blood flow through the lungs The relation between the velocity of blood flow through the lungs and the pulse rate (fig 10) shows considerable variation, but is closer than that between the basal metabolic rate and the pulse rate

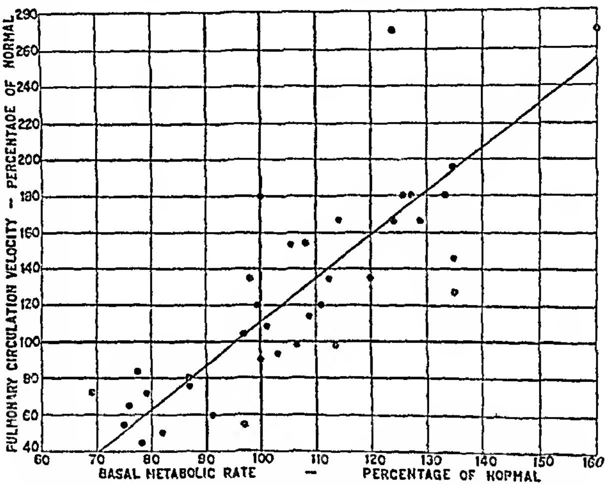


FIG 11 THE RELATION BETWEEN PERCENTAGE VARIATIONS IN THE PULMONARY BLOOD VELOCITY AND BASAL METABOLIC RATE IN PATIENTS WITH MYXEDEMA AND WITH THYROTOXICOSIS

The relation between the basal metabolic rate and the velocity of blood flow through the lungs The relation between the basal metabolic rate and the velocity of blood flow through the lungs is close and shows relatively few variations (fig 11) This close parallelism between blood velocity and metabolism is further evidence that the velocity of blood flow is a fundamental characteristic of the circulation Comparison of the relation between the velocity of blood flow and the basal metabolic rate in myxedema and thyrotoxicosis affords addi-

tional evidence that the increased velocity of blood flow through the lungs in thyrotoxicosis is due to the elevated metabolism rather than to a specific toxic effect on the heart The relation between the basal metabolic rate and the velocity of blood flow is a simple linear one (fig 11). If the mean increase in the velocity of blood flow in thyrotoxicosis were due to a specific toxic effect, the line representing the relation between the velocity of blood flow and basal metabolic rate would be expected to assume a different direction than that for myxedema The fact that the slope is a continuous one is indirect evidence that the increased blood velocity in thyrotoxicosis is due to the increased basal metabolic rate

It should be noted that a given percentage increase or decrease in the basal metabolic rate is accompanied by a far greater percentage change in the velocity of blood flow. This finding is in accord with observations on the relation between the minute volume output of the heart and the basal metabolism in myxedema and thyrotoxicosis (4) (22) (115) (28) (111) This does not necessarily mean that there is a disproportionately increased velocity of blood flow in thyrotoxicosis, or a disproportionate decrease in myxedema, for the comparison involves two different phenomena which are expressed in totally dissimilar units The results demonstrate, however, the close interrelation between the two fundamental physiological characteristics, blood flow and metabolism, and throw additional light on the degree, manner, and results of changes in the circulation associated with increased and decreased metabolic rates

VII THE EFFECT OF EPINEPHRIN ON THE VELOCITY OF BLOOD FLOW

The effect of epinephrin on the velocity of blood flow was studied by Blumgart, Gargill and Gilligan (20) using the radioactive method The basal metabolic rate and velocity of blood flow were measured in normal subjects before and again after the subcutaneous administration of 0 5 to 1 cc of a 1.1000 solution of epinephrin in order to compare changes due to epinephrin with similar changes occurring spontaneously in patients with thyrotoxicosis (18) Epinephrin produced an average increased velocity of blood flow through the lungs of approximately 170 per cent with a rise in the basal metabolic rate of approximately 15 per cent This effect was greater than might be

expected on the basis of the increase in the basal metabolic rate since in thyrotoxicosis such increases in the basal metabolic rate produce a much less striking increase in the velocity of blood flow (18) The velocity of blood flow from the arm to the heart was similarly increased These observations on the velocity of blood flow indicate that the main action of epinephrin is preponderantly upon the heart itself This is in accord with other physiological investigations (45) (61) (72) and measurements by other investigators (53) (137) (57) of the minute volume output of the heart

VIII THE EFFECT OF VARIATIONS IN THE OXYGEN CARRYING CAPACITY OF THE BLOOD ON THE VELOCITY OF BLOOD FLOW

When the oxygen carrying capacity of the blood is diminished as a result of anemia, two mechanisms are available to maintain an adequate supply of oxygen to the tissues (91) These mechanisms may act singly or together The first of these consists in relatively more complete abstraction of oxygen from the blood as it passes through the capillaries (65) Normally, 100 cc of arterial blood contain approximately 18 cc of oxygen Under normal basal conditions only about 5 5 cc are removed from the blood as it passes through the capillaries The remaining 12 5 cc may be considered as reserve oxygen which can be called upon during exercise or other unusual states to prevent asphyxia of the tissues The anemic patient in relying on this mechanism of more complete oxygen abstraction diminishes his reserve oxygen and sacrifices this factor of safety, the degree of sacrifice depending upon the severity of the anemia

The second mechanism which may compensate for a deficient concentration of hemoglobin consists of an increase in blood flow If the concentration of hemoglobin is 50 per cent of the normal, the blood flow may be doubled Under such circumstances, the amount of oxygen abstracted from each cubic centimeter of blood would be one-half the normal, but the total amount of oxygen given off to the tissues would be unchanged and the total reserve oxygen would be undiminished The heart, however, would be required to expend an abnormal amount of energy, and the circulatory reserve would be encroached upon The extent to which the pulmonary blood flow is accelerated in the presence of anemia was studied by Blumgart,

Gargill and Gilligan, using the radio-active method (19) The method appeared particularly suited to the study of the circulatory adjustment to anemia because, in contrast to circulatory minute volume estimations, the measurements are more direct and do not involve elaborate estimations of the CO_2 dissociation curves in each patient as in the carbon dioxide methods All measurements were obtained

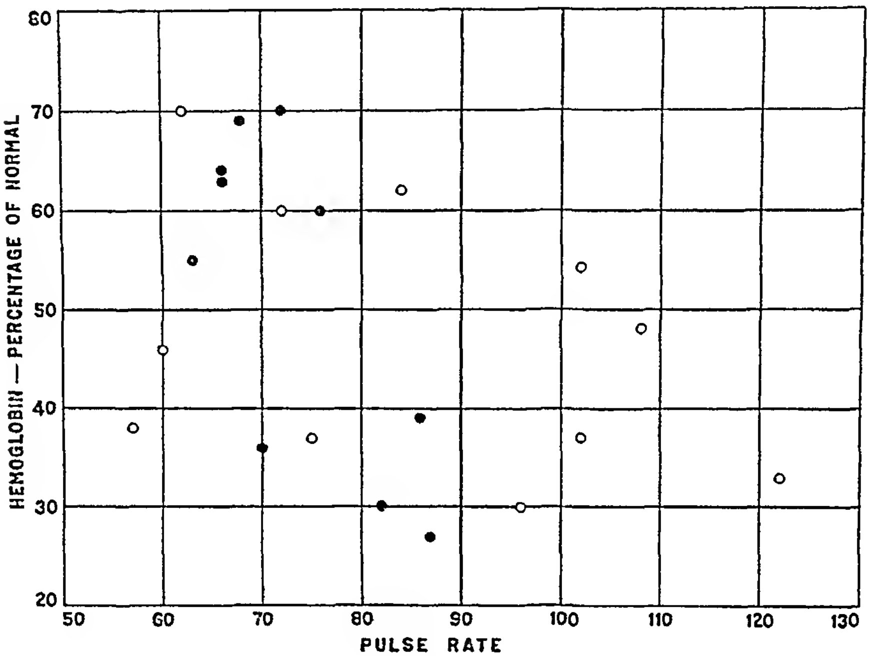


FIG 12 RELATION BETWEEN HEMOGLOBIN CONCENTRATION (PERCENTAGE OF NORMAL) AND PULSE RATE IN PATIENTS WITH "PRIMARY" ANEMIA AND ANEMIA SECONDARY TO DISEASES OTHER THAN CARCINOMA

The solid dots refer to measurements in patients with "primary" anemia, the circles, to measurements in patients with anemia secondary to diseases other than carcinoma

under basal metabolic conditions The hemoglobin concentration of the peripheral blood was measured by the Newcomber method The blood plasma volume was measured by the brilliant vital red method used by Thompson (135) In several patients with pernicious anemia observations were made when the hemoglobin concentration of the blood was low and later when, after treatment with liver extract (100), the blood findings more nearly approached normal

Thirty-two complete series of measurements were made in twenty-nine subjects with pernicious anemia, with secondary anemia and carcinoma, and with secondary anemia due to causes other than carcinoma (19) All patients were free from evidence of congestive heart failure The patients were divided into several groups according to the etiology of the anemia in order to learn whether the circulatory adjustment differed according to the underlying pathology

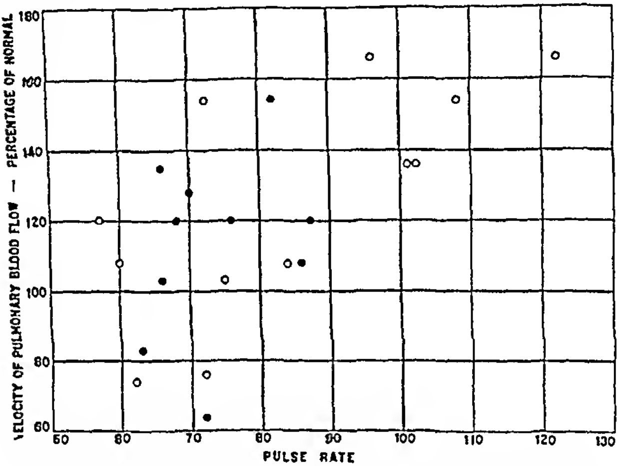


FIG 13 RELATION BETWEEN THE PULSE RATE AND THE VELOCITY OF PULMONARY BLOOD FLOW IN PATIENTS WITH "PRIMARY" ANEMIA AND ANEMIA SECONDARY TO DISEASES OTHER THAN CARCINOMA

The solid dots refer to measurements in patients with "primary" anemia, the circles, to measurements in patients with anemia secondary to diseases other than carcinoma

The circulatory adjustment in patients with primary anemia and anemia secondary to diseases other than carcinoma To clarify the relation between certain important findings, the relation between the hemoglobin and the pulse rate (fig 12), between the pulse rate and the velocity of pulmonary blood flow (fig 13), and the relation between the velocity of pulmonary blood flow and the hemoglobin concentration of the blood (fig 14) were plotted in patients with "primary"

anemia and in patients with secondary anemia not due to carcinoma The results showed that, while there were considerable variations, the velocity of blood flow through the lungs in these patients generally tended to increase in proportion to the degree of anemia The variations might well have been due to small differences in the basal metabolic rate, some investigators having found normal values, others

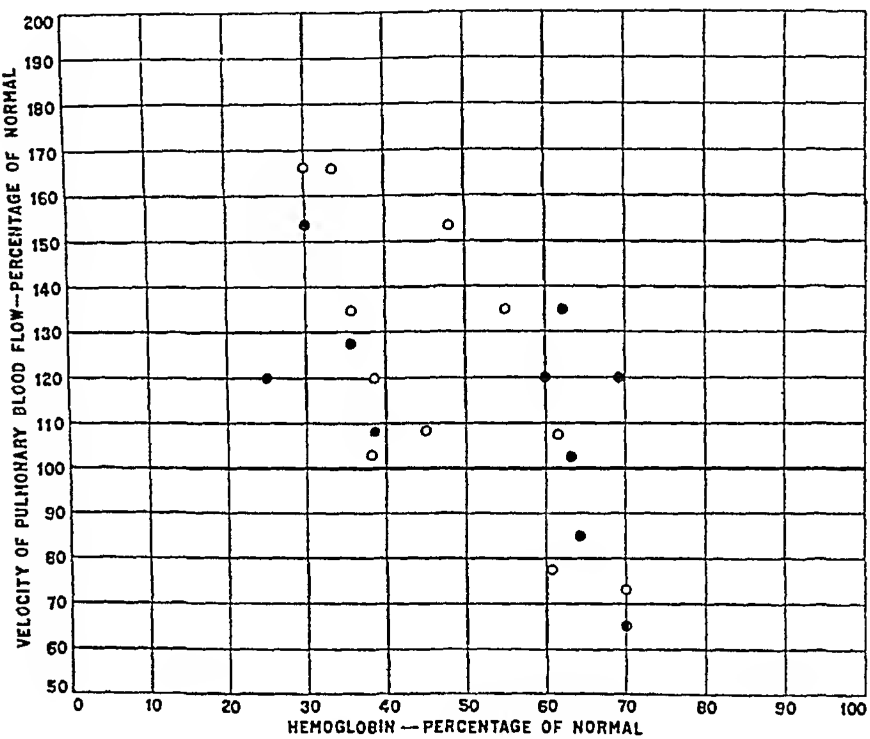


FIG 14 RELATION BETWEEN THE VELOCITY OF PULMONARY BLOOD FLOW AND THE HEMOGLOBIN CONCENTRATION OF BLOOD

The solid dots refer to measurements in patients with "primary" anemia, the circles, to measurements in patients with anemia secondary to diseases other than carcinoma

an increase (48) Studies of the velocity of blood flow in thyrotoxicosis and myxedema demonstrate that the pulmonary circulation time may be affected by the metabolic rate (17) (18) The variations may also have been due in part to the fact that different individuals with anemia probably rely in varying degree on the abstraction of a greater percentage of oxygen from the capillary blood.

These alterations in the velocity of blood flow are in accord with observations on the minute volume output of the heart in anemia Plesch (108), by an indirect method, found that the total blood flow was always increased roughly in proportion to the severity of the anemia Liljestrand and Stenstrom (82) likewise observed a rise in the minute volume output of the heart but believed that, in consequence of the greater oxygen utilization in anemia, the amount of increase was less than that found by Plesch The observations of Richards and Strauss (114) were in entire agreement with the findings of Liljestrand and Stenstrom (82)

Certain investigators have inferred the general state of the circulation in anemia by studying the oxygen content of the arterial and venous blood of the arm (101) (88) It is questionable, however, whether results gained by the study of the blood flow through the arm can rightly be used as an index of the general circulatory adjustment of the body G N Stewart (127) was evidently of similar opinion He found that the blood flow in the arm was diminished in anemic patients but stated that this diminution in blood flow might be due to peripheral vasoconstriction allowing blood flow through other parts of the body to be markedly increased

The vital capacity of the lungs in the patients studied by Blumgart, Gargill and Gilligan (19) was moderately reduced in the absence of any signs of congestive heart failure Some patients complained of weakness and fatigue but these factors, according to Peabody and Sturgis (106), are not important in causing a reduction of the vital capacity of the lungs

The mean plasma volume per kilogram of body weight was within the range of normal, again indicating the constancy of this characteristic of the circulation (21) The mean blood volume per kilogram was moderately decreased

In a study of the response of the circulation to wide variations in basal metabolic rate in myxedema and thyrotoxicosis (17) (18), the pulse rate was observed to be more closely related to changes in pulmonary blood velocity than to changes in the basal metabolic rate Similarly, in patients with anemia, the pulse rate was more closely related to changes in the pulmonary circulation velocity than to variations in the degree of anemia This is in accord with expectation for

the pulse rate and velocity of blood flow are both characteristics of the general circulatory adjustment and as such are more closely related physiologically to each other than to change in the oxygen carrying capacity of the blood

During muscular exercise in normal individuals the minute volume output of the heart rises as a linear function of the oxygen absorption, but at the same time the oxygen utilization is on the whole more complete, though the type of work may to some extent affect the relative degrees to which these two mechanisms are employed (39, 40) In thyrotoxicosis, on the other hand, the compensation is almost entirely circulatory for the oxygen demands of the body are usually supplied without diminishing the oxygen tension of the mixed venous blood although increased oxygen utilization takes place (81) (115) In anemia the greater the diminution in hemoglobin, the greater the extent, even at rest, to which the blood supply must be increased to supply adequate amounts of oxygen to the tissues Under such circumstances, any muscular exercise places a relatively great burden on the cardiovascular system This doubtless is an important factor in the frequent presence of dyspnea in patients with severe anemia, such as pernicious anemia The clinical observations of Herrick (68), Bullrich (26), and Coombs (41) that anemic patients with angina pectoris may be relieved of their attacks of pain by improving the condition of the blood is readily understood on the basis of these considerations The heart may be involved to such a slight extent that it is able to maintain an adequate blood flow provided that the oxygen carrying capacity of the blood is normal In the presence of anemia, however, the increased amount of work necessary to compensate for the condition cannot readily be accomplished, particularly since the blood supply to the heart is affected in common with that of the rest of the body

The circulatory adjustment to secondary anemia in patients with carcinoma Patients with anemia secondary to carcinoma were studied as a separate group because clinical experience suggests that the circulation is frequently affected adversely in this condition Symptoms such as dyspnea, signs of congestive failure, peripheral edema, weakness and cyanosis are frequently more pronounced than one would expect on the basis of anemia, malnutrition or toxicity (35) The

findings in the group of patients studied were in accord with such clinical experience The average concentration of hemoglobin was practically the same in patients with carcinoma as in patients with pernicious anemia, but the velocity of pulmonary blood flow was only 89 per cent of the average normal in the patients with carcinoma in contrast to 113 per cent in patients with pernicious anemia

The pulmonary circulation time and related aspects in two patients with polycythemia vera Since the velocity of blood flow was increased in patients with a diminished concentration of hemoglobin, it was of interest to learn whether the circulation would be slowed in patients with abnormally great concentrations of hemoglobin In contrast to the unusually rapid blood flow found in the former group, two patients with polycythemia vera showed definite retardation of the blood flow beyond the average of normal This slowing in blood flow occurred in spite of the tendency to increased basal metabolism in this condition (65a) In one patient the extent to which the slowing was related to the increased amount of hemoglobin cannot be accurately stated, for, although the patient showed no signs of congestive failure at the time of the test, fibrillation of the auricles was present Blumgart and Weiss (14) observed, however, that in the absence of signs of circulatory failure the blood velocity *may* be normal, even in the presence of this abnormal mechanism The slowing of the blood flow in polycythemia vera corresponded in degree to the diminished minute volume output of the heart observed by Liljestrand and Stenstrom (82) The increase in blood volume is due to the increased number of red blood cells, the plasma volume per kilogram of body weight being greatly diminished below the average of normal (74) The characteristics of the blood are the reverse of those present in anemia and the circulatory adjustment is similarly altered

The findings emphasize the close interrelationship between the respiratory-circulatory-metabolic system Evidence presented in a study of the velocity of blood flow and related aspects of the circulation in pulmonary emphysema suggested that the circulation was accelerated in this condition to compensate for the defect in "external respiration" (144) The results of the study of the velocity of blood flow in anemia indicate that, similarly, the circulation is accelerated to compensate for failure of the "internal respiration"

IX THE VELOCITY OF BLOOD FLOW AND RELATED ASPECTS OF THE CIRCULATION IN PATIENTS WITH CARDIOVASCULAR DISEASE

The occurrence of dyspnea and the reduction of vital capacity are among the first disturbances in cardiac failure and indicate early changes in the dynamics of the circulation of blood through the lungs The physiological and pathological importance of the pulmonary blood flow consequently has always attracted considerable interest but, until recently, the peculiar inaccessibility of the pulmonary vessels has necessitated recourse to animal experimentation for direct observations Unfortunately such experiments reproduce but imperfectly and crudely conditions comparable to clinical cardiovascular disease In man, only indirect observations have been possible by measurements such as the pulmonary minute volume flow according to the principle of Ficke Such observations demand considerable cooperation on the part of the patient and are unsatisfactory in the presence of dyspnea.

Koch (76) in 1922 injected fluorescein into the vein of one arm and, by observing the time of its arrival in the corresponding vein of the other arm, found the circulation time prolonged in patients with edema and other signs of myocardial failure The circulation time of patients in whom circulatory compensation had been reestablished was slightly prolonged in the majority of subjects and was within the limits of normal in a smaller group of individuals Koch's results indicate only a general relationship between the velocity of blood flow and the degree of myocardial failure The limitations of the fluorescein method and the difficulty of estimating the exact onset of the appearance of the material have been discussed earlier in this review.

Blumgart and Weiss (14, 15) in 1928 reported the results of sixty-three measurements of the arm to heart circulation time and the pulmonary circulation time by the radioactive method in fifty-four male patients with cardiovascular disease, and attempted to establish the relationship between the velocity of blood flow and other fundamental aspects of the circulation In each patient the clinical signs and symptoms were noted and the pathologic physiology studied by measurements of the vital capacity of the lungs, of the venous pressure, and of the velocity of blood flow through the lungs and from the arm to the heart The measurements frequently were repeated after definite changes in the clinical condition had occurred

The patients studied were grouped according to the etiology of the cardiovascular disease to learn whether the sequence of events in the development of cardiac failure was always the same or whether it varied according to the etiology of the circulatory disturbance

Patients with rheumatic heart disease

Rheumatic infection of the heart causes its serious effects in at least three ways (*a*) by invasion of the myocardium, (*b*) by deformation of the valves, (*c*) by producing conditions favorable for the occurrence of auricular fibrillation In order to learn the relative importance of these factors in affecting the velocity of blood flow through the lungs and the velocity of the venous blood flow to the right auricle, the patients with rheumatic heart disease were grouped into three classes as follows (*a*) patients convalescent from acute rheumatic fever but without evidence of valvular heart damage, (*b*) patients with rheumatic valvular heart disease with regular rhythm and (*c*) patients with rheumatic valvular heart disease with fibrillation of the auricles

After the clinical subsidence of the rheumatic infection but before evidence of valvular damage appears, the pulmonary blood velocity may be somewhat increased This finding conforms to the other clinical evidences of cardiac hyperactivity such as forcible precordial pulsation, rapid ventricular rate, and flushed skin In one patient the myocardium was evidently severely damaged for there was slowing of the pulmonary blood flow This patient showed no evidence of valvular damage or disturbance of rhythm but had been troubled by increasing dyspnoea for four months and orthopnoea for three weeks He had a rapid ventricular rate, squeaking rhonchi over the bases of the lungs, and a lowered vital capacity The pulmonary circulation time was definitely prolonged (twenty-four seconds), while the velocity of venous blood flow to the right auricle was within the limits of normal (seven seconds)

In patients with compensated rheumatic valvular heart disease and regular rhythm the velocity of blood flow through the lungs was generally normal, the venous pressure was not elevated, and the vital capacity of the lungs was either normal or somewhat diminished When early symptoms of circulatory insufficiency, such as palpitation on exertion, manifested themselves, the vital capacity was reduced

and the velocity of blood flow was definitely retarded, but the venous pressure was frequently still within the limits of normal With the appearance of signs of congestive failure, however, the venous pressure became elevated and the vital capacity and the velocity of blood flow deviated from the normal still further

In patients with fibrillation of the auricles in addition to the valvular heart damage, the slowing in the velocity of blood flow was generally greater (table 3) than in similar patients with regular rhythm, and it should be noted that practically all the subjects with auricular fibrillation had suffered from severe circulatory decompensation and showed symptoms or signs of congestive failure at the time of test. The slowing in blood flow in these patients probably was due in large part

TABLE 3

Averages of findings in patients with rheumatic valvular disease compared to the normal

	REGULAR RHYTHM	AURICULAR FIBRILLATION	NORMAL
Arm to heart time, seconds	9	12	6 6
Pulmonary circulation time (crude), seconds	12	26	10 8
Venous pressure, cm water	9	14	7 3
Vital capacity per square meter, cc	2,068	1,704	2,376

All but one patient with regular rhythm were compensated All patients with auricular fibrillation had suffered from severe circulatory decompensation and showed symptoms or signs of congestive failure at the time of test

to myocardial damage, for in other subjects in whom the myocardium was functionally competent the velocity of blood flow was normal, and no signs or symptoms of circulatory insufficiency were present in spite of the totally irregular rhythm

Patients with syphilitic heart disease

In patients with syphilitic heart disease there is a decrease in the velocity of blood flow through the lungs which parallels the clinical evidences of circulatory failure except that paroxysmal dyspnoea and precordial pain do not seem to be associated with quite as much slowing of the blood stream as observed in patients with rheumatic heart disease This suggests that paroxysmal breathlessness and pain in patients with syphilitic aortitis may be due in part to a reflex

mechanism or to transitory functional disproportion between the right and left chambers of the heart The arm to heart circulation time observed by Blumgart and Weiss in the patients with syphilitic heart disease showed an average relative shortening of seven seconds This finding of a relatively rapid peripheral blood flow even with slowing in the pulmonary circulation is evidence of the late appearance of failure of the right chambers of the heart in this form of cardiac disease and is in harmony with general clinical experience The left auricle and ventricle labor under a great handicap in aortic insufficiency and seem to give way sooner than the right chambers, which in the earlier stages, are still capable of receiving all the venous blood from the periphery and transferring it into the pulmonary vessels This situation contrasts with the early strain of the right ventricle

TABLE 4

Averages of circulatory measurements in patients with arteriosclerosis

	VITAL CAPACITY	VITAL CAPACITY PER SQUARE METER	PULMONARY CIRCULATION TIME (CRUDE)	ARM TO HEART TIME	VENOUS PRESSURE
	cc	*cc*	*seconds*	*seconds*	*cm H_2O*
No history of cardiac failure and no signs of congestive failure	3,190	1,946	16 1	6 6	2 4
Dyspnoea on exertion but no signs of congestive failure at time of test	3,070	1,803	22 2	12 2	2 2
Signs of congestive failure at time of test	1,450	861	46 7	24 2	13 2

in mitral stenosis and insufficiency Consequently peripheral stasis may occur in patients with mitral stenosis while the left ventricle is still functionally capable, whereas in patients with aortic insufficiency, peripheral stasis is a sign of failure of all the chambers of the heart This consideration of events explains why peripheral stasis occurs so late in aortic insufficiency and why its occurrence is of such grave prognostic import

Patients with arteriosclerosis and myocardial degeneration

In patients with arteriosclerosis measurements of the pulmonary circulation time and vital capacity show departures from normal values that generally parallel the clinical symptoms and signs, although this relation does not necessarily hold in each instance (Table 4)

Patients with arterial hypertension

The velocity of blood flow in patients with arterial hypertension but without circulatory failure is either normal or slightly slowed, while with the appearance of congestive failure a retardation in the pulmonary and peripheral blood flow occurs which is similar to that observed in patients with a corresponding degree of circulatory failure but with a normal arterial blood pressure The slowing in blood flow in the absence of signs or symptoms of circulatory failure in some patients may be related to back pressure effects of arterial hypertension on the pressure within the pulmonary vessels There is experimental evidence for this idea Cloetta and Staubli (34) found that compression of the thoracic aorta always caused an increased lung volume, and Straub (130) and also Gerhardt (59) likewise observed that increased arterial pressure in the greater circulation produced an increase in the volume of the lesser circulation Such an increase in the amount of blood in the lungs would lead to increased cross sectional diameter of the stream of blood flowing through the lungs Slowing in blood flow with prolongation of the pulmonary circulation time would then occur since the velocity of flow is inversely proportional to the cross sectional diameter of a stream Observations by Wearn, Barr and German (143) are in accord with this hypothesis, for they observed in animals that slight compression of the abdominal aorta caused considerable dilatation of alveolar capillaries

In no patient with hypertension was an abnormally rapid velocity of blood flow observed This observation suggests that the fundamental disturbance in arterial hypertension is increased peripheral resistance rather than cardiac hyperactivity

X THE GENERAL RELATION BETWEEN THE VELOCITY OF BLOOD FLOW, THE VENOUS PRESSURE AND THE VITAL CAPACITY OF THE LUNGS IN PATIENTS WITH CARDIOVASCULAR DISEASE COMPARED WITH SIMILAR MEASUREMENTS IN NORMAL PERSONS

In the following general statistical treatment of the data obtained in the various studies by Blumgart and Weiss (15), an attempt will be made to learn the extent and frequency of changes in the velocity of blood flow, the venous pressure, and the vital capacity of the lungs in all subjects with cardiovascular disease compared with similar measurements in normal persons

Changes in the venous pressure, in the velocity of blood flow, and in the vital capacity of the lungs can be compared with each other only if obtained in the same subjects Such comparison would almost certainly be erroneous, if, for example, variations of venous pressures of some patients with cardiovascular disease were compared with variations of the vital capacities of other patients with cardiovascular disease, for it would be impossible to be certain that such different groups showed exactly the same degree of cardiovascular damage Consequently, only those patients are included here in whom all three measurements were obtained Duplicate measurements in the same subject have been excluded in order not to weight some of the results unduly

Since measurements of the velocity of blood flow, of the venous pressure, and of the vital capacity of the lungs are expressed in such dissimilar units as seconds, centimeters of water, and cubic centimeters of air per square meter of body surface, since the order of magnitude of the measurements differs widely, and since, moreover, the vital capacity diminishes, the venous pressure rises, and the pulmonary circulation time and the arm to heart time becomes greater in circulatory insufficiency, comparison of such unlike quantities is difficult All measurements have, therefore, been reduced to a common basis by expressing them in terms of percentage variation from their normal average In all diagrams (see fig 15) the measurements have been classified in 10 per cent groups The shaded columns, for example, between +5 and −5 indicate the number of subjects in whom the measurements were found to be within the limits of +5 and −5 per cent of the average of the entire normal group Vital capacity measurements were first expressed in the number of cubic centimeters per square meter of body surface The percentage of the normal average was then calculated If, for example, the vital capacity of a given individual was 1782 cc per square meter of body surface, and the normal average 2376 cc per square meter of body surface, the vital capacity observed would be 75 per cent of the normal, or, as we have charted it, a percentage deviation from the normal of −25 per cent Similarly, the actual venous pressure has been calculated in terms of percentage of the average normal and the variation of this percentage from the normal charted

Expression of the pulmonary circulation time and of the arm to heart time in terms of actual velocity presented a somewhat different problem The "circulation time" denotes the time necessary for a substance to travel between two arbitrarily fixed points, the longer the time necessary, the slower is the speed of the substance To express this inverse relation between circulation time and velocity it was necessary to divide the average normal pulmonary circulation time by the one observed in order to secure an estimate of the speed in terms of the normal percentage The normal average pulmonary circulation time is eleven seconds, and if, for example, the observed time in a patient with cardiovascular disease were twenty-two seconds, the doubling of the circulation time denotes a slowing of the blood stream to one-half the normal average velocity A circulation time of twenty-two seconds would therefore be charted as −50 per cent The data relating to the arm to heart times have been similarly treated

In these diagrams the normal measurements are those obtained in fifty subjects studied, and the data in patients with cardiovascular disease are those presented in communications of Blumgart and Weiss (9, 10, 11, 13, 14) The group of patients with cardiovascular disease includes those whose circulation was compensated, as well as those whose circulation was insufficient

The frequency distribution of the pulmonary circulation time The diagram (fig 15) shows the degree and frequency of variations in the pulmonary circulation times in fifty patients with cardiovascular disease compared with the findings in fifty normal persons A frequency distribution diagram such as the one presented is of value in showing the degree and incidence of variations in the velocity of blood flow in cardiovascular disease compared to the normal For purposes of diagnosis, the ideal test would be one according to which all results in diseased states differed from any found in normal subjects The degree to which a test approaches this ideal is one measure of its diagnostic importance It is consequently of interest that of the fifty patients with cardiovascular disease, twenty showed more marked diminution in the velocity of pulmonary blood flow than that found in any single normal subject of this series

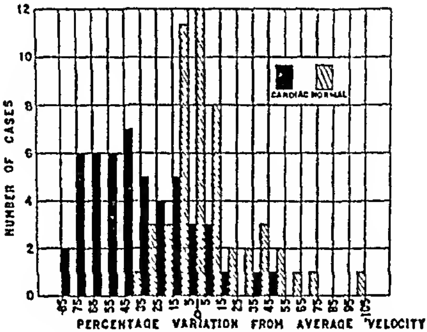


FIG 15 COMPARISON OF PULMONARY CIRCULATION TIMES OF FIFTY NORMAL AND FIFTY CARDIAC SUBJECTS

The frequency distribution of the vital capacity of the lungs (per square meter of body surface) The percentage variation in the normal subjects and in patients with cardiovascular disease has been charted (fig 16) In the normal subjects the range of the vital capacity variation is less than that of the pulmonary circulation time, but it should be noted that in the cardiovascular patients likewise there is a

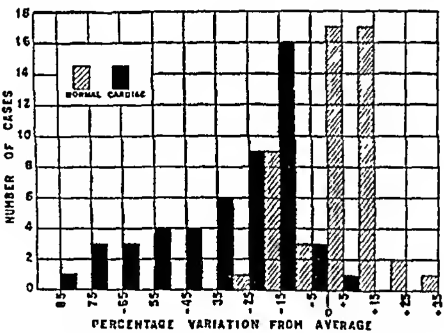


FIG 16 COMPARISON OF THE VITAL CAPACITIES OF THE LUNGS IN FIFTY CARDIAC AND FIFTY NORMAL SUBJECTS

sımılar relatıon, the devıatıon from the normal average pulmonary cırculatıon tıme ıs correspondıngly less strıkıng Although twenty cardıac patıents showed more marked dımınutıon ın the velocıty of pulmonary blood flow than that found ın the lowest normal subȷect (fig 15), only fifteen patıents showed more marked dımınutıon ın the vıtal capacıty than the lowest normal

The frequency dıstrıbutıon of the arm to heart tımes The dıagram (fig 17) shows the degree and frequency of variatıon ın the arm to heart tımes ın fifty patıents wıth cardıovascular disease compared wıth the findıngs ın fifty normal persons In contrast to the measurements

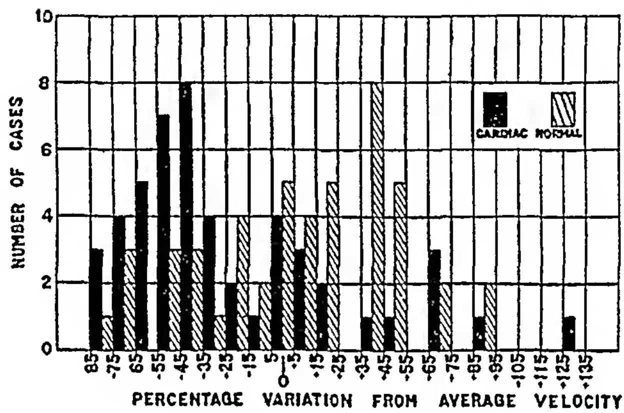


Fig 17 Comparison of Arm to Heart Times of Fifty Cardiac and of Fifty Normal Subjects

of the vıtal capacıty and of the pulmonary cırculatıon tımes, the normal arm to heart tımes show a much greater varıatıon (fig 17) Whıle the normal vıtal capacıtıes of the lungs per square meter varıed over a range of 70 per cent and the pulmonary cırculatıon tımes, wıth one exceptıon, over 120 per cent, the arm to heart times of normal persons varıed over a range of 180 per cent Not only ıs the spontaneous varıatıon of the arm to heart tıme ın normal subȷects great, but the varıatıon ın cardıovascular subȷects ıs practıcally ıdentıcal except that the ıncıdence of the ıncreased tımes (dımınıshed velocıty) ıs somewhat greater ın cardıovascular dısease Thıs findıng of such great dıfference ın the normal arm to heart tıme ıs ın harmony wıth the studıes of G N Stewart (127) and Hewlett and Van Zwaluwenburg (69) who observed that the volume flow of the arm varıed consıderably

The frequency distribution of the venous pressure Inspection of the chart (fig 18) which compares the venous pressures of the fifty patients with cardiovascular disease with the venous pressures in normal persons shows that in both groups of subjects the variability is far greater than that shown by the other measurements The venous pressure in cardiovascular disease varied over a range of some 360 per cent, in normal subjects over some 300 per cent Of the fifty normal subjects, thirty showed a venous pressure below the average, twenty, a venous pressure above the average In cardiovascular

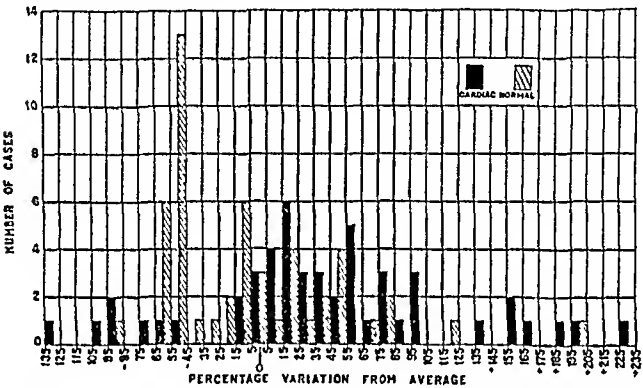


Fig 18 Comparison of Venous Pressures of Fifty Cardiac and Fifty Normal Subjects

disease twelve measurements were below the average, thirty-eight above the average Analysis of these findings confirms the general impression that congestive failure is attended by a significant rise in venous pressure, but that this rise cannot be interpreted as diagnostic because of the great variability shown by normal persons

The relation of the crude pulmonary circulation time to the vital capacity of the lungs in normal persons and in patients with cardiovascular disease The frequency distribution of the vital capacity and of the crude pulmonary circulation time discussed above does not indicate whether those individuals who showed a lower vital capacity also tended to

show a pulmonary circulation time greater than the average normal (decreased velocity) To study the relationship between the pulmonary circulation time and the vital capacity of the lungs more clearly, a diagram (fig 19) has been constructed The chart is divided into four parts by a vertical and a horizontal line The horizontal line represents the average normal pulmonary circulation time The vertical line represents the average normal vital capacity found in fifty normal persons Group 1 consists of individuals in each of whom a short pulmonary circulation time was associated with an

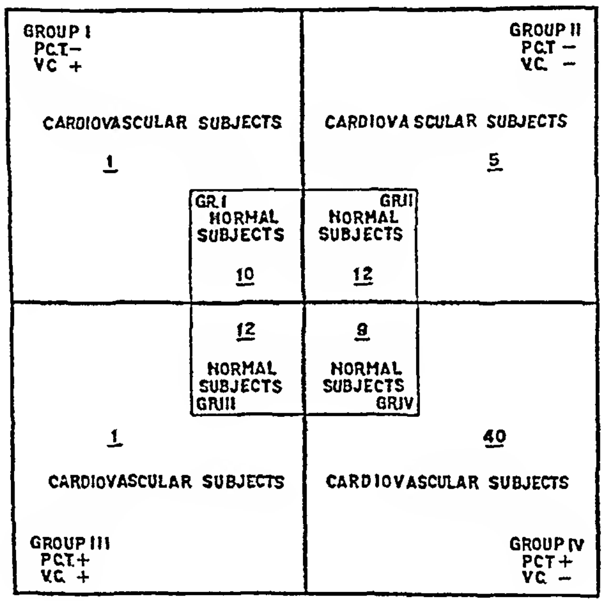


FIG 19 THE RELATION OF THE VENOUS PRESSURE TO THE CRUDE PULMONARY CIRCULATION TIME AND TO THE VITAL CAPACITY OF THE LUNGS

increased vital capacity, group 2, of persons in each of whom a short pulmonary circulation time was associated with a lowered vital capacity, group 3, of persons in whom a prolonged pulmonary circulation time (decreased velocity) was associated with an increased vital capacity, and group 4, of persons in whom a prolonged pulmonary circulation time was associated with a diminished vital capacity The normal subjects of each group are included in the smaller squares, the subjects with cardiovascular disease, in the

larger squares The normal subjects are distributed fairly evenly into the four groups so that the probability of a given normal individual being in any one group is about equal Quite the reverse is true of patients with cardiovascular disease They show a striking tendency to be in group 4 (prolonged pulmonary circulation time and decreased vital capacity)

According to the results shown in figure 19, the probability of a given individual with a low vital capacity (groups 2 and 4) having cardiovascular disease could be expressed by

$$\frac{\text{Group 2 cardiovascular plus Group 4 cardiovascular}}{\text{Group 2 normal plus Group 4 normal}}, \text{ or } \frac{45}{21}$$

That is to say, roughly, the probability, regardless of the pulmonary circulation time, would be two to one Similarly if the pulmonary circulation time were prolonged (groups 3 and 4), indicating a slower velocity of pulmonary blood flow, the probability of the subject having cardiovascular disease regardless of the vital capacity of the lungs would be $\frac{41}{21}$, or again, roughly two to one If, however, both tests were performed and the pulmonary circulation time were found prolonged and the vital capacity diminished (group 4), the probability of the subject having cardiovascular disease would be expressed by

$$\frac{\text{Group 4 cardiovascular}}{\text{Group 4 normal}}, \text{ or } \frac{40}{9} \text{ or approximately four to one}$$

These considerations are important since they indicate that, in contrast to the arm to arm circulation time, the pulmonary circulation time is prolonged at the same time that the vital capacity of the lungs becomes lowered

Statistical study of data, such as is presented here, is important in physiological study of the dynamics of the circulation, for it throws considerable light on the general relation between the velocity of blood flow, the vital capacity of the lungs and the venous pressure under both normal and pathological conditions In an individual instance these considerations are of limited interest It is not for a moment proposed that such formulae should be used in the diagnosis and prognosis of circulatory disease These will, in fact, usually depend on the

physical examination and history On the other hand, the general knowledge of the velocity of the peripheral and pulmonary blood flow in different types of cardiovascular disease is of considerable value both physiologically and clinically In certain obscure cases the electrocardiograph and the vital capacity of the lungs give useful information and it is felt that the measurement of the velocity of blood flow similarly may be of value since it affords a more direct measurement of the cardiac and vascular response in appropriate pathological conditions

XI. THE RELATION BETWEEN RETARDATION IN THE VELOCITY OF BLOOD FLOW AND THE APPEARANCE OF DYSPNOEA

Clinical observations have shown that in patients with heart disease the velocity of pulmonary blood flow and the vital capacity of the lungs is less than normal, and that the decrease is definitely related to the degree of circulatory failure Peabody (105) has shown that the decrease in the vital capacity bears a close relation to the development of dyspnoea, and statistical analysis of the available data of Blumgart and Weiss (15) indicates that the decrease in the vital capacity and the slowing in blood flow occur at about the same time in the development of circulatory insufficiency and definitely precede the rise in peripheral venous pressure The suggestion has been made that the reduction in the vital capacity may be related to an increase of pressure in the pulmonary circulation with engorgement of the alveolar capillaries of the lungs (124) As a result of observations on cats, in which the pulmonary veins were obstructed, Drinker, Peabody and Blumgart (47) stated that it is apparent that the lungs act as a slightly elastic sponge and are able to take up a vast amount of blood without significant pressure change As the alveoli are extremely vascular such a condition might produce a stiffening or "Lungenstarrheit," in the sense of von Basch (141), which would interfere with their easy expansion and collapse in respiration Similarly, the moderately prolonged pulmonary circulation time frequently found in patients with dyspnoea but without physical signs of congestive failure (14) suggests that increased filling of the pulmonary vessels with an increase in the functional cross section of the flowing stream occurs very early in circulatory insufficiency Measurements of the minute

volume output of the heart are in accord with this concept (2, 86, 87, 93)

A study of the anatomical and physiological characteristics of the veins affords an explanation of why the vital capacity is reduced and the velocity of blood flow is lessened before a rise in venous pressure occurs The walls of the veins contain but little muscular tissue and may be considered as easily collapsible, but inelastic, tubes They are freely distensible, therefore, until the limit of their capacity is reached and only when this limit is reached are they resistant to further stretching During the stage of increasing venous filling in myocardial failure added amounts of blood result in very small increases in venous

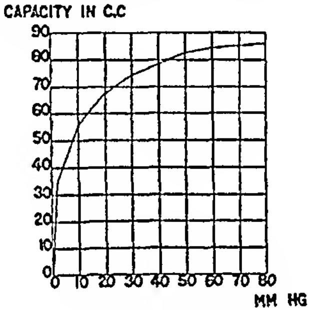


FIG 20 CURVE OF DISTENSIBILITY OF A VEIN (BY E H STARLING FROM FIGURES GIVEN BY ROY)

pressure Once, however, the vessels are filled with blood to the limit of their capacity, these relatively inelastic tubes can expand no further and any additional amounts of blood flowing into the veins will then result in a conspicuous rise in pressure This is graphically illustrated by figure 20

These facts indicate that a stage of engorgement precedes an increase of pressure in the veins and only after the veins have become filled to the limit of their capacity do additional amounts of blood cause a rise in pressure In normal resting persons the veins are not filled to their full capacity and so they are partially collapsed Their cross sectional area is, therefore, smaller than when they are fully distended

Since the velocity of flow is inversely proportional to the cross sec-

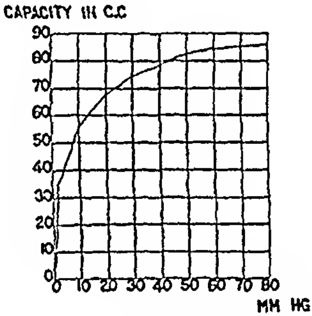
physical examination and history On the other hand, the general knowledge of the velocity of the peripheral and pulmonary blood flow in different types of cardiovascular disease is of considerable value both physiologically and clinically In certain obscure cases the electrocardiograph and the vital capacity of the lungs give useful information and it is felt that the measurement of the velocity of blood flow similarly may be of value since it affords a more direct measurement of the cardiac and vascular response in appropriate pathological conditions

XI THE RELATION BETWEEN RETARDATION IN THE VELOCITY OF BLOOD FLOW AND THE APPEARANCE OF DYSPNOEA

Clinical observations have shown that in patients with heart disease the velocity of pulmonary blood flow and the vital capacity of the lungs is less than normal, and that the decrease is definitely related to the degree of circulatory failure Peabody (105) has shown that the decrease in the vital capacity bears a close relation to the development of dyspnoea, and statistical analysis of the available data of Blumgart and Weiss (15) indicates that the decrease in the vital capacity and the slowing in blood flow occur at about the same time in the development of circulatory insufficiency and definitely precede the rise in peripheral venous pressure The suggestion has been made that the reduction in the vital capacity may be related to an increase of pressure in the pulmonary circulation with engorgement of the alveolar capillaries of the lungs (124) As a result of observations on cats, in which the pulmonary veins were obstructed, Drinker, Peabody and Blumgart (47) stated that it is apparent that the lungs act as a slightly elastic sponge and are able to take up a vast amount of blood without significant pressure change As the alveoli are extremely vascular such a condition might produce a stiffening or "Lungenstarrheit," in the sense of von Basch (141), which would interfere with their easy expansion and collapse in respiration Similarly, the moderately prolonged pulmonary circulation time frequently found in patients with dyspnoea but without physical signs of congestive failure (14) suggests that increased filling of the pulmonary vessels with an increase in the functional cross section of the flowing stream occurs very early in circulatory insufficiency Measurements of the minute

volume output of the heart are in accord with this concept (2, 86, 87, 93)

A study of the anatomical and physiological characteristics of the veins affords an explanation of why the vital capacity is reduced and the velocity of blood flow is lessened before a rise in venous pressure occurs The walls of the veins contain but little muscular tissue and may be considered as easily collapsible, but inelastic, tubes They are freely distensible, therefore, until the limit of their capacity is reached and only when this limit is reached are they resistant to further stretching During the stage of increasing venous filling in myocardial failure added amounts of blood result in very small increases in venous



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tional area, a slowing of the velocity of venous blood flow would occur when the veins are fully distended, provided that the increase in the cross sectional area of the blood stream were not counterbalanced by an increase in the pressure gradient within the vessels Starling showed that the latter possibility is unlikely, and the observations of Blumgart and Weiss (9, 10, 11, 14) are opposed to such a consideration The slowing of the blood flow in the veins during the period of increased venous engorgement might, therefore, be expected to precede, as in fact it does precede, the occurrence of increased venous pressure

Similar events occur, in all probability, in the lungs With engorgement and distention of the pulmonary vessels (46), increase in the total cross sectional area of the blood stream through the lungs may well take place This would explain why slowing in the pulmonary *velocity of blood flow has been observed to occur so early in circulatory* failure, even before the clinical signs of congestive failure appear.

Clinical experience and velocity of blood flow measurements contribute several facts which are in harmony with the theory that the interference with the ventilation of the lungs which manifests itself by a decreased vital capacity, and the slowing in pulmonary blood flow which shows itself by a prolonged pulmonary circulation time, are due to chronically increased filling of the pulmonary veins and capillaries In accordance with these considerations mitral stenosis is characterized by an early onset of the tendency to dyspnoea and an associated low vital capacity In aortic insufficiency, on the other hand, the tendency to dyspnoea occurs relatively late and the vital capacity remains high until a relative mitral insufficiency develops and the pulmonary circulation is affected

XII RELATION BETWEEN THE VELOCITY OF BLOOD FLOW FROM THE ARM TO THE HEART AND THE APPEARANCE OF PERIPHERAL EDEMA

It is worthy of note that in some patients, even with slowing of the blood flow through the lungs and with reduction in the vital capacity, the peripheral venous blood flow may be well within the limits of normal according to the measurements by Blumgart and Weiss (14) of the venous pressure and the velocity of the venous blood from the right antecubital vein to the right auricle Excepting one patient who had suffered congestive failure shortly previous to his tests, and

another patient who had slight pitting edema on the day of the test, the arm to heart times of the patients with syphilitic heart disease averaged 6 5 seconds (average normal, 6 6 seconds), while the pulmonary circulation times averaged 17 0 seconds (average normal, 10 8 seconds) These findings contrast with the observations in patients with mitral stenosis in whom slowing of the peripheral blood flow occurred earlier The absence of peripheral edema associated with normal arm to heart times suggests that the difference between so-called "dry heart failure" and "congestive heart failure" may be due to differences in the velocity of the peripheral blood stream

The relation between the appearance of edema and the slowing of the peripheral blood stream indicated by the arm to heart time is again strikingly evident in the measurements in patients with arteriosclerosis and myocardial degeneration (11) The patients without edema had an arm to heart time of 15 seconds or less, while those with edema showed an arm to heart time of 18 seconds or more The relation between the arm to heart time and the appearance of edema is only a general one since the arm to heart time is an index of the velocity of blood flow of the arm, whereas edema usually appears first elsewhere The appearance of edema probably does not coincide quantitatively with a definite degree of slowing in the blood stream for it is also dependent on physico chemical changes which are influenced by many other factors

XIII RELATION BETWEEN DECREASE IN BLOOD FLOW AND THE ORTHOPNEA OF CONGESTIVE HEART FAILURE

Observations demonstrate that with a rise in the cerebral venous pressure, the intracranial blood flow tends to diminish, thereby favoring increased anoxemia of the respiratory center Hill (71) stated that any increase in general venous pressure caused a slowing of cerebral blood flow In animals (42, 152) (153), a definite slowing of the velocity of intracranial blood flow has been observed following elevation in the intracranial venous blood pressure Influenced by these facts, Ernstene and Blumgart (51) therefore proposed a theory of orthopnea according to which the orthopneic position benefits the patient with congestive circulatory failure because it secures a maximum blood flow about the respiratory center and thereby relieves the

patient from the distress due to partial asphyxia in that area The mechanism of this was conceived to be as follows Physiological investigations (3) indicate that the blood flow in the capillaries is dependent on the pressure gradient in these vessels The greater the difference in pressure along the capillary the greater the blood flow An elevation of the venous pressure, therefore, diminishes capillary blood flow in the absence of any striking increase in arteriolar blood pressure Other factors remaining equal, increased venous pressure leads to stagnation of blood in the capillaries and so produces stagnation anoxemia

The orthopneic position would relieve the increased pressure within the veins about the respiratory center in the following manner There are no efficient valves in the veins between the cerebral capillaries and the right auricle (71) If a patient with uncomplicated cardiovascular failure and a venous pressure at the right auricle equivalent to 15 cm of water lay flat in bed, there would be a corresponding pressure of 15 cm of water in the veins about the respiratory center This would result in diminished blood flow in the capillaries and stagnation anoxemia in this region If, however the patient sat up, so that the respiratory center would be 15 cm above the right auricle, the pressure in the veins about the center would be zero The velocity and volume of blood flow through the vessels leading to these veins would thereby be increased, the respiratory center would receive more adequate supply of blood, and the subjective respiratory distress would be relieved

This concept of the pathologic physiology of orthopnea was supported by the results of the study of twenty-two patients with uncomplicated myocardial failure of the congestive type Direct measurement of the velocity of intracranial blood flow in man is not feasible so indirect evidence was obtained by measuring the venous pressure and the degree of orthopnea (51) A parallelism between the degree of orthopnea and the average amount of elevation in the venous pressure was observed in the course of eighty-two measurements in these patients Simple elevation of the head by flexion of it on the thorax when the patient was flat in bed also produced a conspicuous diminution of respiratory distress in all but one instance

In addition to the evidence presented, certain clinical phenomena

and the following observations of other investigators support the venous pressure theory of orthopnea Wolff and Blumgart (152) observed in animals that a definite slowing of the velocity of intracranial blood flow resulted from elevation of the intracranial cerebrospinal fluid pressure A rise in cerebrospinal fluid pressure is accompanied by an increase in cerebral venous pressure because the skull is a closed cavity without elasticity The pressures of the cerebrospinal fluid and venous blood must closely approach each other It therefore may be assumed that Wolff and Blumgart would have observed the same slowing of velocity of blood flow if the cerebral venous pressure had been raised directly instead of indirectly by increasing the intracranial pressure This work therefore demonstrates the validity of the basic assumption of the venous pressure theory of orthopnea, namely, that an increased general and cerebral venous pressure diminishes the cerebral capillary blood flow

Salathe (120) applied a tambour to the fontanel of an infant 6 weeks old and observed that on his placing the child in a vertical position with the feet down the intracranial pressure fell, and that on his turning the child to a posture with the feet up the pressure rose Brissaud and Franck (25) observed the same changes of pressure in a patient in whom a large portion of the skull had been removed Hill (70) found that the intracranial pressure of a patient who had been trephined was negative while the man sat upright, but became positive as soon as the head was bent down toward the knees or on any expiratory effort All these observations indicate that in man intracranial pressure and therefore cerebral venous pressure is diminished by changing from the recumbent to the sitting position

It is well recognized that, in patients with myocardial failure, cyanosis of the face and lips increases in the recumbent position or may appear only in that position (89) (6) It is probable that this cyanosis is due in large part to retarded capillary blood flow and stagnation anoxemia Since such alterations occur in the superficial capillaries in the recumbent position, it is reasonable to suppose that comparable changes take place simultaneously in the capillaries about the respiratory center In both locations, the decreased capillary blood flow undoubtedly results from the local increase in venous pressure in the recumbent position This together with the observed correlation

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between the height of venous pressure and the degree of orthopnea suggests that in patients with myocardial failure the elevated position provides relief mainly by releasing the respiratory center from the effects of increased venous pressure, and so secures maximal blood flow in that region The correlation between the height of venous pressure and the degree of orthopnea suggests further that these patients at all times tend to maintain an elevation which is sufficient to keep the respiratory center above the meniscus of the column of venous blood extending upward from the right auricle In this way, the flow of blood in the capillaries in the region of the respiratory center is kept as normal as possible with the existing myocardial failure

It is a common clinical observation that in patients with congestive failure the jugular veins are engorged as high as the angle of the jaw in the recumbent position, but when the upright posture is assumed the column of blood is visible for only a short distance above the clavicle Similar changes occur when the head is flexed on the thorax in the recumbent position This indicates that any elevation of the head reduces the cerebral venous pressure and therefore the venous pressure about the respiratory center This observation and the relief experienced in the recumbent position when the head is elevated strongly support the venous pressure theory of orthopnea Of all the theories of orthopnea, only the venous pressure theory and Sahli's (119) hypothesis of the effect of gravity on cerebral venous congestion can explain the relief experienced by the patient on flexing the head on the thorax As the position of the thorax and abdomen is unchanged when the head is elevated, the increased comfort cannot be due to an alteration in the amount of blood in the lungs Similarly, the relief cannot be attributed to increased efficiency of the abdominal and thoracic accessory muscles of respiration, to changes in reserve air, middle capacity or vital capacity of the lungs, or to alterations in lung expansion

It may be contended that according to the hypothesis of Ernstene and Blumgart (51) a normal person should suffer from intense dyspnea due to increased venous pressure when the head is held lower than the rest of the body The work of Wolff and Blumgart (152) indicates, however, that, in such subjects, the increased venous pressure is balanced by either an increased arterial pressure or arteriolar dilata-

tion In either case, the normal pressure gradient in the capillaries would be maintained In patients with circulatory failure, however, vasodilatation is already present, and an increase in arterial pressure in all probability does not take place because the heart is affected The cyanosis of the face observed in normal persons when the head is held lower than the rest of the body may well be related to the type of cyanosis observed by Goldschmidt and Light (60) in which no change in the venous oxygen unsaturation took place

The evidence accumulated by Ernstene and Blumgart from their own observations and from the investigations of others (153) is in accord with the venous pressure theory of orthopnea It should be recognized, however, that some of the factors considered as of primary importance by other investigators undoubtedly contribute to the relief experienced in the sitting position The more complete oxygenation of the blood in the lungs in the upright as compared with the recumbent posture (62) (56) presumably aids in securing the relief experienced by the patient in the former position Furthermore, in those patients who show an important increase in vital capacity of the lungs on changing from the recumbent to the sitting posture (31), this increase may be responsible, in part, for the comfort obtained In patients with ascites (119), the upright position undoubtedly affords relief partly because this position facilitates diaphragmatic movements It is believed, however, that in all patients with congestive heart failure and increased venous pressure, the relatively low cerebral venous pressure obtained in the sitting position is the primary factor in reducing the respiratory discomfort

XIV THE EFFECT OF DIGITALIS ON THE VELOCITY OF BLOOD FLOW THROUGH THE LUNGS

The nature of the action of digitalis has been extensively studied in an attempt to establish more accurately the precise advantages and limitations of the drug The problem has been complicated by the assumption, expressed or implied, that the results and inferences of experiments on normal dogs directly indicate the clinical action of digitalis on the abnormal heart of man (64) The following discussion will consequently be limited to the results of observations on man

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In studying the action of digitalis in man, observers have measured changes in certain fundamental characteristics of the circulation both before and after administration of the drug (38, 36, 27) The pertinent question has been put, "Shall beneficial action depend on the a priori assumption that it can be recognized and can be appraised in terms of one or another detailed effect of this drug, such as its effect on the blood pressure or the volume output or its effect on tone or on contraction or another of the many actions which it undoubtedly possesses?" (37) While the effect on the circulation as a whole must always differ from the sum total of the effects on the various fundamental characteristics of the circulation, measurements of these individual characteristics and a study of their relationships constitutes the most valid means of laying down the basis of rational therapeutics at the present time

More than six hundred measurements in man in health and in disease have demonstrated that the velocity of blood flow is of fundamental importance and that abnormal slowing occurs with the development of congestive failure, while clinical improvement is attended by an increase in the speed of blood flow The clinical improvement and the attendant increased velocity of blood flow in patients with cardiovascular disease followed the administration of digitalis in the majority of instances The effect of the digitalis bodies on the velocity of blood flow in normal subjects as well as in patients with cardiovascular disease was measured by Weiss and Blumgart (145), and the relation of these findings to changes in the vital capacity of the lungs, the venous pressure and other clinical manifestations was studied

Normal subjects Strophanthin and tincture of digitalis were administered intravenously and by mouth to eight normal persons The effect on the velocity of pulmonary and peripheral venous blood flow, on the vital capacity of the lungs and on arterial and venous blood pressures was observed Amounts of these drugs corresponding to large therapeutic doses failed to change appreciably the velocity of pulmonary blood flow and the other above mentioned aspects of the circulation in normal subjects

Patients with cardiovascular disease Of eight patients who had symptoms or signs of congestive failure even at rest, six showed a definite increase in the velocity of blood flow following the administra-

tion of digitalis bodies These results derive additional significance from the fact that before the administration of digitalis all subjects were kept in bed eight to thirty days until clinical observations, electrocardiographic measurements, and tests of the vital capacity indicated no further improvement Of six patients who showed no signs or symptoms of congestive failure at rest, two showed an increase in the velocity of blood flow, three showed no appreciable change, and one showed a slowing in the velocity of blood flow after digitalis In only three of the fourteen patients with cardiovascular disease, therefore, was the blood flow slowed after digitalis, and it is significant that two of these three patients showed auricular fibrillation with a normal ventricular rate before the drug was administered

The effect of digitalis on normal persons and on patients with cardiovascular disease, as well as the data elicited from numerous other observations described previously in this review, demonstrates that digitalis, unlike epinephrin, has no specific stimulating effect on the circulation but tends to increase the speed of blood flow only when the latter is abnormally slowed This can, of course, be effected only when the heart is still capable of an increased response

The fact that the normal subjects studied by Weiss and Blumgart (145) showed no appreciable alteration in the velocity of blood flow after digitalis, and that the patients with symptoms and signs of congestive failure when at rest exhibited a greater tendency to show an increase in the velocity of the pulmonary blood flow after digitalis than patients whose hearts were compensated at rest (145) is in harmony with the concept that the digitalis bodies tend to increase the velocity of blood flow toward, but not above, normal This was again found by Weiss and Ellis (147) who studied four patients with rheumatic heart disease who were compensated at rest both before and after digitalis The arm to face circulation time, the cardiac output per minute and per beat, the circulating blood volume and the vital capacity of the lungs showed no significant changes after the administration of the drug

The change in velocity of blood flow resulting from digitalis is therefore the same as the change which follows other therapeutic measures which are beneficial in the treatment of circulatory failure To condemn the use of digitalis because it fails to improve the circula-

tion in a few patients is as irrational as giving up the use of arsenicals because they do not always improve patients with syphilis

XV THE VELOCITY OF BLOOD FLOW AND ITS RELATION TO OTHER ASPECTS OF THE CIRCULATION IN PATIENTS WITH PULMONARY EMPHYSEMA

Pulmonary emphysema frequently presents one of the most perplexing problems of differential diagnosis in clinical medicine because the cardinal symptoms, dyspnea, cough and cyanosis are also characteristic of circulatory insufficiency. In many patients, the history and signs of cardiac pathology enable one to make a diagnosis of cardiovascular disease with confidence, but in others, with little or no evidence of heart disease and with no signs of peripheral congestion, the problem arises as to whether the dyspnea of the patient is due to early myocardial failure or to the disordered gaseous exchange of pulmonary emphysema Frequently, the problem is still further complicated by the simultaneous presence of both conditions (107) It then becomes a matter of considerable clinical importance to estimate the relative significance of these two conditions in producing the cough, dyspnea and lowered vital capacity, because proper treatment and accurate prognosis require such differentiation.

Unfortunately, our knowledge of the underlying pathologic physiology of pulmonary emphysema (121), upon which rational diagnosis and therapeutics must be based, is incomplete Studies on the circulation in patients suffering from pulmonary emphysema are especially lacking since direct measurement of the blood flow through the lungs has hitherto been impossible and indirect measurements of the minute volume flow are not feasible since the methods postulate normal gaseous exchange

In twenty-one of the twenty-five patients with pulmonary emphysema studied by Weiss and Blumgart (144) the velocity of blood flow was within the limits of normal. The clinical condition of the patients varied considerably. Some complained of weakness and dyspnea only on exertion, others suffered from intense dyspnea and cyanosis at rest Chronic bronchitis, bronchial asthma, and structural and functional changes in the thorax appeared to play a predominant rôle in the etiology of emphysema in this group The normal or even increased

velocity of blood flow, particularly in those patients who had many of the symptoms and signs of severe circulatory failure, such as conspicuous weakness, cyanosis and dyspnea, is of great importance It shows that pulmonary emphysema alone is sufficient for the production of these symptoms and signs The normal venous pressures in these patients is in agreement with this finding

Severe pulmonary emphysema, therefore, does not necessarily obstruct the pulmonary circulation sufficiently to interfere with the normal velocity of blood flow On the contrary, in some patients increased speed of blood flow through the lungs may be present On the basis of the facts now available one cannot say whether the normal or increased velocity observed in these patients is maintained with or without aid of the cardiac reserve Circulation and ventilation are closely related physiologic mechanisms in the human body The significance of hyperventilation in compensating for circulatory failure is fully appreciated A reverse relation between circulation and ventilation possibly exists in pulmonary emphysema

In a small group of four subjects studied by Weiss and Blumgart (144), slowing in the velocity of blood flow with elevation in the peripheral venous pressure indicated that, in these patients, pulmonary emphysema was complicated by circulatory failure The degree of slowing of blood flow was less than that in patients with arteriosclerosis who had never exhibited congestive failure and whose only complaint was dyspnoea on exertion While such slowing of the blood flow in patients with cardiovascular disease was associated with but slight restriction of muscular activity, the patients with pulmonary emphysema were completely incapacitated The conspicuous symptoms and signs shown by these patients were due, therefore, only to a slight extent to changes in the blood flow In one patient the opportunity presented itself of following the condition closely and correlating the findings with the post mortem examination The patient suffered from the extreme form of the disease The velocity of blood flow was measured only two months before her death, which was directly due to emphysema The patient also showed myocardial failure, as judged from pitting edema around the ankles, but the crude pulmonary circulation time was only 19 5 seconds The dyspnea, retraction of the lower ribs on inspiration, and the weakness could not be explained

on the basis of retardation in blood flow The fact that this patient practically choked to death with but slight slowing of the blood stream and the fact that other patients with emphysema did not show marked slowing suggest that, with the defective aeration of blood due to ventilatory insufficiency such as is present in emphysema, conspicuous reduction in blood flow due to cardiac failure would probably be incompatible with life This is in accord with the clinical observation that elderly people, with a tendency to emphysema and with cardiovascular disease, show a more severe disturbance in bodily function than one would expect from the cardiovascular damage alone

Because the clinical signs and symptoms may not aid in differentiating emphysema from myocardial failure and, furthermore, because emphysema and myocardial failure may both be present in a given patient, combined measurements of the vital capacity, venous pressure and pulmonary blood flow may be of great importance in estimating the relative extent of pulmonary and cardiac disease.

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BILIRUBINEMIA

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CONTENTS

INTRODUCTION

The recent advances in the knowledge of the group of diseases in which there is impairment of bilirubin excretion, have been made through the cooperation of chemists, physiologists, pathologists and clinicians, and these painstaking investigations, particularly during the last thirty years, have enabled us to build the foundations of our present conception of the problem of jaundice The older views on jaundice, which were based only on anatomical grounds, have been recently so thoroughly revised, that the writer feels it will be best to pass in review some of the outstanding physiological and chemical researches, before dealing with the methods of determination of bilirubinemia and its clinical applications

CHEMICAL ORIGIN OF BILIRUBIN

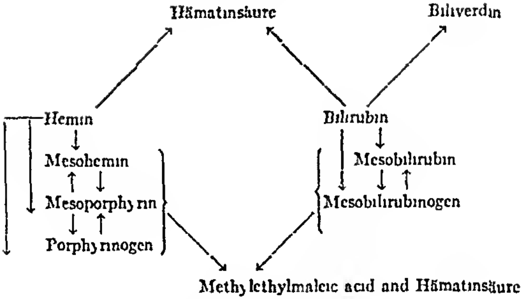
Virchow (272) in 1847 was the first to suggest the chemical similarity of bilirubin and hemoglobin, for he discovered in old foci of hemorrhage

a pigment closely related to bilirubin, to which he cautiously gave the name of "hematoidin" Three years later Herrmann (103) demonstrated that intravascular hemolysis, by means of the injection of distilled water, would lead to the subsequent excretion of bilirubin in the urine Tarchanoff (261) extended these observations by injecting hemoglobin itself intravenously, and collecting the excreted bile through a biliary fistula An increased output of bile resulted The chemical identity of the pigment formed when hemoglobin is liberated intravascularly (bilirubin) and the pigment formed when hemoglobin is liberated extravascularly (hematoidin) now seems well established as a result of the experiments of Rich and Bumstead (224) on a sample of hematoidin found in an old hemorrhagic cyst

Many attempts, not altogether successful, have been made to produce bilirubin from hemoglobin in vitro, the painstaking researches of Fischer (72), Thannhauser (262, 263) and Kuster (138) being specially noteworthy

Nencki and Zaleski (202) succeeded in producing a substance which they called "hemopyrrol" by treating hematin ($C_{34}H_{32}O_4N_4FeCl$) with powerful reductants This hemopyrrol was found by Kuster (138) to be composed actually of a mixture of different pyrrols (iso-hemopyrrol and cryptopyrrol) accompanied by the corresponding pyrrol carbonic acids Treating hematin afterwards by oxidants, Kuster produced an acid "hamatinsaure" (methylcarboxyethyl maleic acid) The initial product obtained is the imido form of this acid which, under the influence of alkalies, loses its NH_3, giving the anhydrid correlated to the "hamatinsaure" As the formula of this "hamatinsaure" contains the characteristic pyrrol nucleus, found in the pyrrolic acids derived from hematin by reduction, it can be concluded that by treating hematin either with strong oxidants or reductants similar products can be formed Treating bilirubin with the same reagents, Kuster (139) and Fischer and Meyer (73) obtained the same two pyrrol groups and pyrrol-carbonic acids, as well as the tribasic hematic acid (Hamatinsaure)

Briefly these processes can be tabulated, as suggested by Fischer, as follows

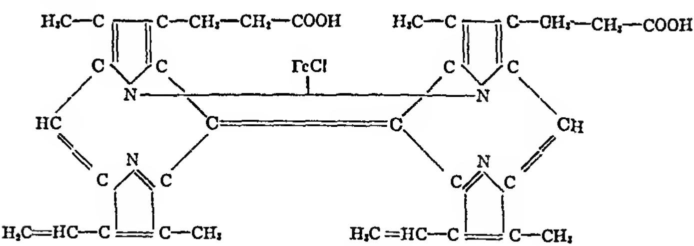


(arrows pointing upwards = oxidation)
(arrows pointing downwards = reduction)

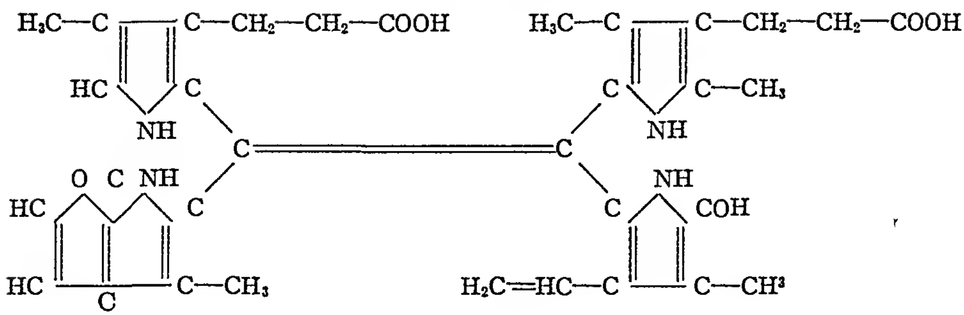
As these reactions constitute a series of hydrolytic processes, Kuster simplifies them in the following schematic formula

$$\text{Hematin} + 2H_2O = \text{Bilirubin} + FeO$$

The relation between the pigments of the blood and bile is further *indicated by the accompanying structural formulae for hemin and* bilirubin, according to the views of Fischer, which have been recently confirmed by his brilliant studies on the synthesis of hemin and porfirins (75)



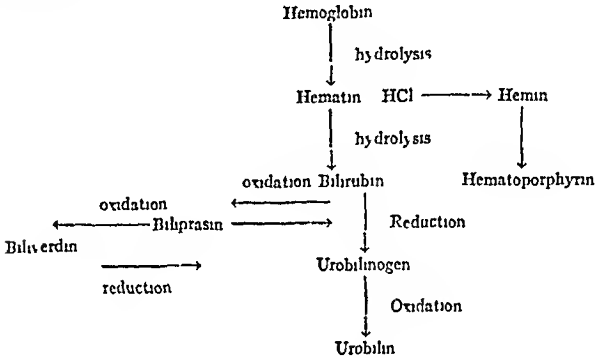
Hemin



Bılırubın

Blood hemoglobın seems therefore to be the maın source of supply for the formatıon of bılırubın It ıs possıble that other compounds, contaınıng the pyrrol nucleus ın theır structure, could be changed ınto bılırubın Whıpple and Hooper (284, 285), and more recently Whıpple and Robscheıt (286), state that myohemoglobın ıs another source of bılırubın If Kennedy and Whıpple's statement (125), that blood hemoglobın and muscle hemoglobın are ıdentıcal, sınce both gıve sımılar spectrophotometrıc curves, ıs confirmed, ıt ıs obvıous that muscle hemoglobın may also take part ın bılırubın formatıon Whıpple and Hooper's assertıon that the output of bılırubın ın dogs ıncreases after a dıet rıch ın carbohydrates has been denıed by Inlow (115), and Rous (237), who reported that ın theır experıments wıth bıle fistula dogs, a dıet rıch ın carbohydrates had no effect upon the amount of bıle pıgment formed There ıs a close relatıonshıp between the chlorophyll molecule and hematın (Wıllstater and Stoll (282)), and Noack (204), ın beautıful experıments, has recently shown that bılıpurpurın, a pıgment present ın small amount ın the bıle of hervıborous anımals, has essentıally the same chemıcal constıtutıon as photopheophıtın, a pıgment derıved from chlorophyll Thıs would favor the possıbılıty of an exogenous orıgın of bılırubın The statement of Bollmann, Sheard and Mann (24) that they were unable to detect any alteratıon ın bılırubın formatıon after the ıntravenous ınjectıon of chlorophyll ın dogs, does not exclude the possıbılıty of bılırubın formatıon from chlorophyll, sınce, ın the case of ıntravenous ınjectıons, the excretory power of the lıver rapıdly frees the blood of the ınjected pıgment

The following table taken from Rolleston and McNee (231) gives a short summary of the relationship of bilirubin, and its derivatives, to hemoglobin



PHYSIOLOGICAL ORIGIN OF BILIRUBIN

Since Rich's splendid review (225) on the formation of bile pigment, few facts have been brought to light bearing upon the exact origin of bilirubin

Virchow's original view (272) which came as a consequence of his observation on hematoidin, was that bilirubin could be formed outside the liver, as the pigment he found in old blood extravasations, had a close resemblance to bilirubin The celebrated experiments of Minkowski and Naunyn (186) on the absence of jaundice in hepatectomized geese, in which intravascular hemolysis had been produced by arseniureted hydrogen, were so widely accepted for a time, that the liver came to be considered as the only site of bile formation The work of Minkowski and Naunyn remained unchallenged until McNee (183, 184), repeating and confirming their experiments, explained them in a very different way, stating that the prevention of icterus was probably due to the removal by the hepatectomy of the phagocytic Kupffer cells, rather than to the loss of the polygonal cells of the liver The remarkable series of studies of Mann and his coworkers (160–164) on the physiology of the liver, in which they demonstrated the ap-

pearance of bilirubin in the blood of hepatectomized dogs, an observation amply confirmed by Makino (159), Rich (226) and others, proved conclusively that in dogs, at least, bile pigment continues to be formed, and to accumulate in the blood stream, after the liver, or, indeed, after all the abdominal viscera have been removed (Rich)

As a consequence of these fundamental observations attention was directed towards the extrahepatic formation of bilirubin Lepehne (148) attempted to prove that the pigment is formed by the reticulo-endothelial cells, stating that after overloading these cells with collargol the process of bile pigment formation was less active Rich (227), by the methods of tissue culture, was able to prove that only mesodermal, and not ectodermal or endodermal cells can transform hemoglobin into bile pigment and that this process occurs within the cells Numerous attempts by Rich and Bumstead (224) to prove the existence of some extracellular enzyme which can influence the transformation of hemoglobin into bilirubin, gave uniformly negative results It is therefore probable than when bilirubin is formed from hemoglobin within the phagocytic cells, as in Rich's experiments, the process is carried on by a cellular hydrolytic ferment

Confirming Van den Bergh's early investigations, Ernst and Szappanyos (61) and Komori and Ywao (134) observed the formation of bilirubin following the injection of hemoglobin into the perfused, asphyxiated spleen, and Mann, Sheard, Bollman and Baldes (161) reported that the injection of hemoglobin into the blood, entering the spleen and bone marrow, produces an increase in the amount of bilirubin formed at these sites Mann, Sheard and Bollman (162) measured the relative amounts of bilirubin formed in the liver, spleen and bone marrow, concluding that in dogs the spleen produces more bilirubin than the liver, that even in the absence of the liver and spleen, bilirubin continues to be formed at its normal rate, which would lead to the conclusion that the bone marrow can take over the function of bilirubin formation in the absence of the other sources of formation Whether bilirubin formation can be inhibited by suppression of the bone marrow has not yet been determined

All these concordant experiments seem to prove conclusively that there is an extrahepatic origin for bile pigment It is true, that recently Melchior, Rosenthal and Licht (182, 234, 235), working in

Naunyn's laboratory, in a series of papers revert to Minkowski and Naunyn's original hypothesis, and consider the liver as the main organ of bilirubin formation Their conclusion was drawn from the fact that the jaundice, which invariably follows the injection of toluilendiamine in control dogs, does not appear in hepatectomized animals When the liver is removed, after jaundice has appeared as a consequence of toluilendiamine injection, the bilirubin in the blood not only ceases to increase but actually decreases These facts, however, are not actually incompatible with the extrahepatic origin of bilirubin, for Joanovick and Pick (117) and others, have shown that toluilendiamine produces necrosis of the liver cells This form of jaundice is therefore dependent upon the presence of the liver, as we shall see below, but not in the sense that the liver cell produces the pigment

In summary it can be stated that

1 There is no evidence that the polygonal liver cells are concerned with the formation of bilirubin All the experiments performed in recent years are decidedly against such evidence

2 There is no evidence that there exists an extracellular enzyme capable of transforming hemoglobin into bilirubin It is probable, though not conclusively proved, that this process is carried on by a cellular hydrolytic enzyme

3 The cells of the reticulo-endothelial system are in all probability actively concerned in the formation of bilirubin

METHODS OF BLOOD BILIRUBIN ESTIMATION

Since the classical researches of Gilbert and his associates, many methods have been suggested for the determination of bilirubin in the blood They can be divided into the following groups

1 Estimation based on the oxidation of bilirubin
2 Direct comparative estimation of the colour of blood serum
3 Methods based on the use of Ehrlich's diazo-reagent
4 Spectrophotometric methods

1 Methods based on the oxidation of bilirubin

Gilbert, Herscher, and Posternack (84), in 1903, were the first to elaborate a method for the estimation of serum bilirubin Oxidizing

the bilirubin into biliverdin by means of Gmelin reagent, and comparing the intensity of the colour reaction, they were the first to demonstrate that bilirubin was normally present in the blood serum Later, Hertzfeld (105) applied the same principle using Hammarsten's reagent (1 volume of 25 per cent HNO_3 + 19 volumes 25 per cent HCl, after 24 hours add to 1 volume of this solution, 4 volumes of alcohol), but his figures are subject to the same sources of error as Gilbert's estimations More reliable and simple is the method proposed by Fouchet (78), who oxidizes the bilirubin by a solution containing trichloroacetic acid and $FeCl_3$ (trichloroacetic acid, 5 grams, $FeCl_3$ 10 per cent, 2 cc, distilled water, 20 cc) Equal parts of serum and reagent are taken, the reagent being added to the serum drop by drop, after stirring with a glass rod, the green colour obtained is compared with a previously made colour chart The sensitivity of the method according to Fouchet is $1 \times 60{,}000$ The methods of Posselt (214) and Biffi (21) are based on the same principle of oxidation of bilirubin by acids

The figures obtained using these methods are not reliable, not only because the comparisons with the artificial standards are too roughly approximate, but chiefly because the methods are not sensitive enough

2 Direct comparative estimation of the colour of blood serum

Assuming that the yellow colour of the blood serum is principally due to bilirubin, methods have been evolved to determine the amount of bilirubin by comparing the colour of the serum with artificial standards of approximately the same shade of yellow colour

Meulengracht (179), who was the originator of these methods, employs a standard solution containing 1 10,000 of potassium dichromate plus 2 drops of H_2SO_4 per every 500 cc of solution He dilutes the serum with physiological salt solution until the colours can be compared He obtains thereby a comparative figure which he calls the colorimetric index, giving 1 to 10 units as a normal index [1] The same technique has been recommended under the name of "icterus index" by Maue (170)

[1] For example, if 1 cc of serum is diluted to 25 cc and the standard read 17 5 when the unknown is set at 20, the icterus index is 21 9

and Bernheim (19) They use the colorimeter for the comparison, their calculation being

$$\frac{\text{Reading of standard}}{\text{Reading of unknown}} \times \text{dilution} = \text{icterus index}$$

They state that the normal icterus index lies between 4 and 6 Walter (273) uses, as a standard, a mixture of potassium bichromate (1 10,000) 100 cc and "orange poirier" (1 10,000) 2 cc He employs plasma instead of serum

Ernst and Forster (62) precipitate the serum with two volumes of acetone, and after filtration, they make the comparison in a colorimeter with the dichromate standard so diluted as to make a proper colorimetric reading

As the chemistry, the amount and the daily variation of the lypochromes (lutein, carotin, etc) of the blood is unknown the writer is of the opinion that these methods in which bilirubin as well as all other yellow substances also present in the blood serum are estimated, ought to be discarded It is well known that the yellow colour of the serum increases with a diet rich in vegetables Stoner's (257) studies on carotinemia, so common in children, Fiessinger, Walter, and Thierry's (66) studies on the effect of carotinemia on xanthochromia of plasma, and Rabinowitch's (218) and Hess and Myers' (108) reports of high carotinemia in diabetic patients as well as Hernando's (102) contribution on pseudo-jaundice from carotin pigment should warn the clinician against the employment of the colour of blood serum as an index to bilirubinemia

3 *Methods based on Ehrlich's reaction*

Ehrlich, as early as 1883 (55), discovered that a mixture of sulfanilic acid, HCl and sodium nitrite (diazonium salt) gave a red violet colour when added to solutions containing bilirubin The chemistry of the reaction remained unknown until 1900 when Proscher (217) clearly established the fact that bilirubin combines with the diazobenzolsulphochloride (Ehrlich's diazo reagent) to form acetophenolazorubin, whose formula and spectral bands in different solutions he determined More recently, Kerppola and Leikola (124) describe 13 different stages of oxidation, when Na nitrite and HCl were added to

bilirubin dissolved in chloroform They show that the colour of Ehrlich's diazo-reaction is due partly to oxidation and partly to the action of acid Notwithstanding the importance of Ehrlich's discovery and Proscher's demonstration of the specificity of such a reaction for the estimation of bilirubin, it was only many years later, in 1913, that Van den Bergh and Snapper (270) employed Ehrlich's diazo-reaction for the estimation of blood bilirubin Van den Bergh and his co-workers, by the adaptation of Ehrlich's diazo test to the determination of bilirubinemia, opened up an entirely new approach to the experimental investigation of bile pigment metabolism This test is not only of great assistance because of its delicacy and accuracy in quantitative work, but also because qualitative differences in the behaviour of the reaction serve to differentiate various forms of jaundice

Qualitative Van den Bergh reaction Van den Bergh and Muller (266) discovered that in some cases of jaundice, especially those of the obstructive type, the red violet colour develops immediately after the addition of Ehrlich's diazo-reagent to the blood serum, while in other cases, namely, those of hemolytic nature, the addition of alcohol is necessary to produce the formation of diazo-bilirubin This led to their well known separation of the reaction into the "direct" type, characteristic of obstructive or "mechanical" jaundice, and the "indirect" type, characteristic of non-obstructive or "dynamic" jaundice Feigl and Quarner (64) have further pointed out that besides these two types of reaction, there is a "biphasic reaction" which will be described later

Everyone who has had experience with the Van den Bergh reaction has been able to confirm Feigl and Quarner's type of biphasic reaction, a distinction important to retain, especially when following the progress of jaundiced patients

Technique of the Van den Bergh reaction Collection of blood Blood serum or plasma is equally suitable As it is more difficult to avoid hemolysis when blood is allowed to clot, plasma is most convenient, using 0 2 cc of a 10 per cent solution of potassium oxalate (evaporated to dryness) for 10 cc of blood as anticoagulant (There are no differences in the readings whether plasma or serum is used) The blood has to be fresh as the bilirubin oxidizes on standing and the quality of the reaction may change Test tubes and pipettes used have to be *perfectly* clean

Reagents —

Solution A

Sulphanilic acid	0 1 gram
Concentrated HCl	1 5 cc
Distilled water	100 cc

Solution B

Sodium nitrite	0 5 gram
Distilled water	100 grams

Both solutions ought to be renewed every 15 days

To perform the reaction one mixes 5 cc of solution A and 0 1 5 cc of solution B (This mixture has to be freshly made)

Qualitative reaction One cubic centimeter of oxalated plasma (or serum) is placed in a small test tube and 0 5 cc of the diazo-reagent added The appearance and development of the colour reaction is watched and timed

Direct reaction The colour appears immediately after the addition of the reagent and acquires its maximum intensity 30 seconds later

Biphasic reaction The colour reaction appears at once as in the first type or within 30 seconds but its *maximum intensity* is reached after a variable time If the colour reaches its maximum intensity quite rapidly the reaction is called "prompt biphasic," while it is called "delayed biphasic" when the colour deepens quite slowly

Indirect reaction The colour reaction appears one or more minutes after the addition of the reagent The maximum intensity is reached at variable times and the addition of alcohol is essential to obtain the maximum colour

Quantitative determination Standard solution The standard employed is a solution of cobaltous sulphate If dryed anhydrous cobaltous sulphate is used, take 21 610 grams in 1000 cc of distilled water If crystallized cobaltous sulphate is used ($CoSO_4 7H_2O$), take 39 150 grams in 1000 cc of distilled water This standard is taken by Van den Bergh as equal to 1 unit This corresponds to $\frac{1}{200\,000}$ of bilirubin, i e, 0 5 mgm per cent

A Serum or plasma giving indirect reaction Take 1 cc of serum and 2 cc of alcohol (96 per cent) Shake and centrifuge One cubic centimeter of the supernatant fluid is taken into a test tube and 0 25 cc of the reagent and 0 5 cc of alcohol added Compare the colour with the standard in any microcolorimeter

Calculation In the first dilution we would have a 1 3 dilution but as a result of the contraction due to alcohol this dilution is only $\frac{20}{7}$. In the second dilution we have $\frac{7}{4}$. The final dilution will be $\frac{20}{7} \times \frac{7}{4} = \frac{1}{5}$

Therefore

$$\frac{\text{Reading of standard}}{\text{Reading of unknown}} \times 5 = \text{units} \times \tfrac{1}{2} = \text{mgm bilirubin per cent}$$

B Serum giving biphasic reaction or low bilirubin content with direct reaction Thannhauser and Andersen's modification is recommended To 1 cc of plasma or serum add 2 5 cc. alcohol (96 per cent) and 1 cc of a saturated solution of $(NH_4)_2SO_4$ Shake and centrifuge

Calculation

$$\frac{\text{Reading of standard}}{\text{Reading of unknown}} \times 4 = \text{units} \times \tfrac{1}{2} = \text{mgm bilirubin per cent}$$

If the colour of the unknown is too strong, dilute with 2 parts of alcohol and 1 part of water

C Serum having high bilirubin content (direct reaction) Mix 0 5 cc plasma or serum and 0 5 cc reagent Add water (varying measured quantities to get a reasonable dilution) and then add alcohol so that the fluid is increased thrice its bulk Centrifuge and read in the colorimeter.

Calculation

$$\frac{\text{Reading of standard}}{\text{Reading of unknown}} \times \text{dilution} = \text{units} \times \tfrac{1}{2} = \text{mgm per cent}$$

Modifications of Van den Bergh's technique Two objections have been raised against the Van den Bergh method

1 That it is extremely difficult to obtain a colour reaction which would be entirely comparable to the standard

2 That during the precipitation of the plasma proteins by alcohol, some of the bilirubin is adsorbed by the protein In regard to the first objection, the writer thinks that the utmost care must be taken not to alter the final pH of the solution As the diazobilirubin responsible for the colour reaction behaves like an indicator dye, its colour changes from the blue at the acid side to the yellow on the

alkaline side When perfectly clean tubes and pipettes are used and the proper amounts of reagents are added, the pH of the final solutions is always around the optimum for the production of the red violet colour and no difficulties are encountered With increasing acidity the colour changes to violet first, then to blue, greenish blue and green (oxidation to biliverdin) When the reaction is toward the alkaline side, the colour becomes red, red brown, and yellow Thannhauser

TABLE 1

Comparative blood bilirubin estimations by the Van den Bergh technique and the Thannhausen and Andersen's modification

TYPE OF VAN DEN BERGH REACTION	SERUM BILIRUBIN		PER CENT OF BILIRUBIN ADSORBED BY THE ALCOHOLIC PROTEIN PRECIPITATE
	Van den Bergh technique	Thannhauser and Andersen's technique	
	mg per cent	*mg per cent*	
I Indirect			
Hemolytic jaundice	8 70	9 00	3 0
Pernicious anemia	2 85	2 95	3 4
Malaria	2 00	2 00	0 0
II Biphasic			
Lobar pneumonia	2 04	3 80	20 0
Catharral jaundice	4 00	6 00	33 0
Arsphenamin jaundice	3 00	4 80	37 0
III Direct			
Gall stones	8 00	14 00	42 8
Carcinoma of pancreasinoma	7 00	13 50	48 0
Cholecystitis	3 62	6 51	29 0

and Andersen (264), Greppy and de Micheli (91) advise the acidification of the solution in order to have a blue colour

The second objection is more serious Van den Bergh himself pointed out that when the proteins of serum giving direct and indirect reaction are precipitated with alcohol, the bilirubin, giving the direct reaction, is more easily adsorbed by the protein precipitate than the bilirubin giving the indirect reaction The figures in table 1 taken from numerous concordant determinations, give a clear comprehension of this different behaviour The plasma bilirubin was estimated by the original Van den Bergh technique (alcohol precipitation) and Thann-

hauser and Andersen's modification (264) in which the protein adsorption is loosened by salting out the proteins by a saturated solution of ammonium sulphate

Thannhauser and Andersen's modification in which all the bilirubin goes into solution is therefore to be recommended especially in cases where there is a biphasic reaction or a high indirect reaction

Enriquez and Sivo (57) raise another objection to the Van den Bergh reaction, namely, that in cases of hypobilirubinemia the high dilution required in Van den Bergh's technique makes a colorimetric reading almost impossible, and they propose the following modification To 0 5 cc of serum they add 0 5 cc of a solution of sodium benzoate caffeine (20 per cent) and 0 2 cc of the diazo-reagent The colour is compared to a standard made with a bilirubin solution (0 01 per cent in N/100 NaOH) They avoid protein precipitate, but their final colloid suspension cannot be compared colorimetrically

4 *Spectrophotometric methods*

Huffner was the first to determine bilirubin in this way but Sheard, Baldes, Mann, and Bollmann used the method more extensively (251) There is no doubt that it is by far the most accurate and sensitive way of measuring bilirubinemia, but the cost of the instrument and the careful technique which it requires, makes it unsuitable for clinical work Mann and his co-workers use the Keuffel and Esser colour analyzer which has the advantage over ordinary spectrophotometers of being easier to manipulate As the percentage of light transmission changes with time, they recommend that the alcoholic solutions of serum bilirubin be prepared, and that the readings of wavelength and percentage transmission be made as rapidly as possible in the region of 430 to 500 Comparing this method with the Van den Bergh method, they find that it is possible to determine the character and the shape of the spectrophotometric curve of bilirubin for a dilution as low as one fiftieth of the smallest amount measurable by the Van den Bergh technique

THE NATURE OF THE VAN DEN BERGH REACTION

The nature of the Van den Bergh reaction has aroused considerable attention, since it is generally agreed that the different types of reaction correspond to perfectly distinct groups of jaundice

Van den Bergh (267) proposed two alternative theories (1) That there may be differences in the chemical composition of the bilirubin normally circulating in the blood stream, and in that of the bilirubin which has passed through the liver cell (2) That in the indirect type of reaction the bilirubin is bound up in some manner with the blood proteins or lipoids so as to prevent it from coupling with the diazo-reagent The advocates of the first theory have accumulated evidence of certain physical and chemical differences between the "direct" and "indirect" types of the Van den Bergh reaction these differences are as follows

First That, as pointed out by Van den Bergh (269) and Andrews (7), the bilirubin of serum giving the direct reaction oxidizes more easily than the bilirubin from the serum giving the indirect reaction

Second That when the proteins of both kinds of sera are precipitated with alcohol, the bilirubin giving the direct reaction is more easily adsorbed by the protein precipitate than the bilirubin giving the indirect reaction (Van den Bergh)

Third That when the two types of sera are shaken with chloroform, the "indirect" bilirubin passes into solution into the chloroform while the "direct" bilirubin does not (Grunnenberg (93))

Fourth That the bilirubin from obstructive jaundice is dialyzable through a collodion membrane, while the bilirubin from hemolytic jaundice is not (Hoover and Blankenhorn (111), Brule, Garban and Weissman (29), Leschke (151))

Andrews, reviewing these differences, concludes that the bilirubin giving the indirect reaction is in fine suspension instead of in true solution, or that possibly it is a polymer of the "direct" type While the first three differences may be verified, the writer has been unable to confirm any difference in the dializability of bilirubin whether from obstructive jaundice or from hemolytic jaundice

Collinson and Fowweather (38), accepting the formula for the composition of bilirubin suggested by Fischer (74), who regards it as an acid with two carboxyl groups, capable of forming salts which will differ in certain properties from the free acids, says "while the bilirubin giving the prompt direct reaction is an alkali salt which we believe is probably the ammonium salt, the form which is responsible for the indirect reaction is the free acid present in the blood in a colloidal state" The

writer has been unable to confirm Collinson and Fowweather's experiments The serum giving the direct reaction could not be converted into one giving the indirect reaction by the addition of hydrochloric acid, and only in rare cases did the addition of ammonia to sera giving the indirect reaction hasten the reaction with the diazo-reagent Davies and Dodds (49), who made an interesting study of the limits of hydrogen ion concentration between which the reaction of the diazo-reagent and bilirubin takes place, state that the indirect reaction is produced by oxidized bilirubin, i e , biliverdin, but biliverdin does not give the Van den Bergh reaction Roberts (230) believed that the "indirect" bilirubin is in free colloidal condition, and the "direct" bilirubin is in combination with some substance "the nature of which is as yet undetermined." Newmann (203) concludes from his experiments that the difference between these two types of the Van den Bergh reaction is due to an underlying chemical difference between the bilirubins.

Among the advocates of the second theory, Adler and Strauss (5), in a series of papers speak of a physico-chemical change in the state of serum proteins, namely a change in the $\frac{\text{globulin}}{\text{albumin}}$ ratio, which, according to them, would be considerably lowered in cases of obstructive jaundice, while it would be normal in hemolytic jaundice Some of the authors' experiments are interesting and have been confirmed by the writer, such as the influence of temperature, the addition of alcohol, of salts of caffein, in accelerating the reaction The assumption that the $\frac{\text{globulin}}{\text{albumin}}$ ratio plays an important rôle in the behaviour of the Van den Bergh reaction is unwarranted, as the Van den Bergh reaction changes from the indirect type into the direct in one, four or five hours after biliary obstruction (Barron and Bumstead) without any change in the G A ratio Feigl and Querner (64) suggest a possible lipoid linkage as an explanation for the indirect type of bilirubin, which Andrews was unable to confirm Levi-Crailsheim (154) supports the theory of protein-linkage stating that serum giving the indirect Van den Bergh reaction will give a direct reaction after digestion with pepsin, pancreatin or even liver extracts The writer has been unable to confirm these findings Neither commercial pepsin nor pancreatic

extract proved to be active, had no effect in accelerating the rate of the reaction. Thannhauser and Andersen (264) state that the addition of bile salts, or mixtures of cholesterol and bile salts, can change a serum giving the indirect reaction into one giving the direct reaction. Adler and Strauss (5), as well as several other investigators, were unable to confirm this statement. Bollmann, Sheard and Mann (24), made an important contribution to the theory of the chemical identity of these two types of reaction by demonstrating that alcohol-acetone solutions, and even aqueous solutions of icteric serum from patients having obstructive and hemolytic jaundice, gave the same curve of light transmission when measured spectrophotometrically. Nevertheless, in their conclusions concerning the difference of these two types of reactions, they state that "it might appear that the direct reaction of obstructive jaundice is due to the retention in the blood of a substance which destroys this linkage of bilirubin with serum."

The writer, while investigating the problem (14), has made use of solutions of bilirubin and normal serum, having thus two controlled factors: bilirubin and serum, each of the same chemical constitution. When sodium bilirubinate, buffered to pH 8.43[2] and giving a direct Van den Bergh reaction is added to normal human blood serum in increasing amounts up to 12 mgm. per cent, a typical indirect reaction is obtained. When the concentration of bilirubin is increased to 16 mgm. per cent, the reaction becomes of the biphasic type, i.e., the colour appears twenty seconds after the addition of the diazonium salt, reaching its maximum intensity two minutes later. When the bilirubin concentration is higher than 16 mgm. per cent, a direct reaction is obtained. The following conclusions can be formulated from these experiments. Some constituent of the serum has a tendency to adsorb bilirubin, and this adsorption of bilirubin prevents the immediate coupling with the diazonium salt. Much has been written in regard to the forces which are operating on the surfaces to cause these adsorption effects. One group of workers has taken the viewpoint that the reactions are purely physical, while others have insisted that the forces are those of chemical union. It is no longer expedient to lay great stress upon this difference, since molecular attraction of every degree

[2] Bilirubin is dissolved in N/20 NaOH and 4 M phosphate mixtures of pH 7.00 added. The bilirubin remains in solution for some minutes only, after which it precipitates.

Monge (194) has found an increase in the bilirubin content of the blood some days after residence at high altitudes The over-activity of the blood forming and blood destroying tissues observed under those conditions, together with the effect of anoxemia to be discussed below might possibly explain this observation.

The hyperbilirubinemia of infants is well known Thus from fifty newborn infants examined, Meyer and Adler (177) found only fifteen without signs of jaundice. The bilirubin content of those infants without jaundice fluctuated from 0 6 to 0 9 mgm per cent in the blood

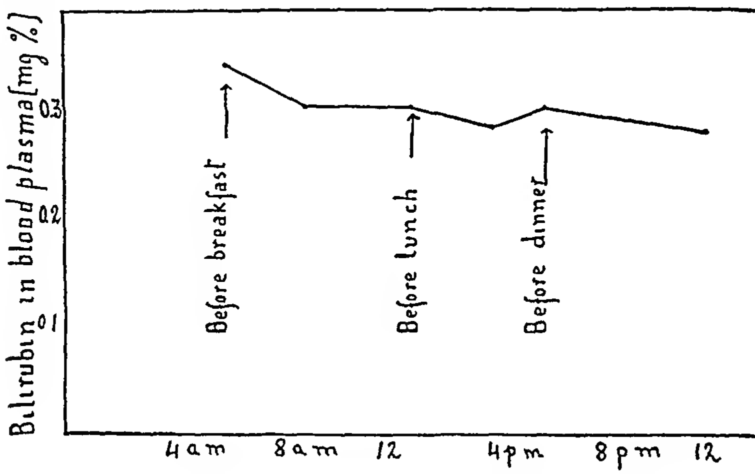


FIG 1 DAILY VARIATIONS OF THE BLOOD BILIRUBIN

taken from the arm, while the blood from the umbilical vein gave higher figures (from 0 9 to 2 1 mgm per cent)

Sex seems to have no influence, although Schiff (252) states that bilirubinemia is higher in males than in females The writer has been unable to confirm this observation

PATHOLOGIC ALTERATIONS OF BILIRUBINEMIA

The maintenance of the concentration of the blood bilirubin within normal limits is a result of the interplay of different factors which enter into the production and excretion of the pigment The number of erythrocytes in the blood and the rate of their destruction, the function of the reticulo endothelial system and the polygonal liver

cells, and the permeability of the bile ducts, are the most important factors for the maintenance of a normal blood bilirubin It follows that any isolated or combined alteration of one or all of these factors will produce a derangement of the normal bilirubinemia, resulting in either an increase or decrease of blood bilirubin

1 *Hypobilirubinemia*

Hypobilirubinemia has not received careful clinical attention, due to lack of sensitive methods of estimating minute amounts of bilirubin in the blood This condition is found in all secondary anemias where the blood lost by hemorrhage is not promptly replaced It can also be associated with alterations of the hematopoietic system (diminution of the number of red blood cells thrown into the general circulation) which have as a consequence a diminished production of bilirubin

A state of hypobilirubinemia is found in the following pathologic conditions (1) In chronic nephritis without cardiac complication (Landau and Held (146)), (2) in malignant tumours without liver metastasis or compression of the ductus choledochus, and (3) in seconday anemias, aplastic anemias, chlorosis Murphy (198) in 34 cases of secondary anemia due to different conditions, finds a consistent hypobilirubinemia The diagnostic value of hypobilirubinemia in the differentiation of pernicious anemia (hyperbilirubinemia) from aplastic or secondary anemia and malignant tumours is now well recognized

2 *Hyperbilirubinemia (jaundice)*

When the amount of bilirubin in the blood rises above 0 5 mgm per cent a condition of hyperbilirubinemia is reached If this hyperbilirubinemia rises above 2 mgm per cent and lasts for some days, bilirubin diffuses through the blood capillaries giving to the skin and mucosas the characteristic yellow colour which constitutes the basis of the clinical syndrome, jaundice

A state of jaundice can be produced by two main processes which will enable us to divide this syndrome into two groups (1) *Obstructive jaundice*, where the primary and initial cause of this syndrome depends on obstruction to the normal bile excretion This group can be easily recognized by chemical tests, i e, *direct* Van den Bergh reaction on

the blood serum, presence of bilirubin in the urine, absence or scarcity of bile pigments in the stools (2) *Non-obstructive jaundice* where the primary and initial cause of the syndrome depends upon a deficiency of the bilirubin excretory function of the polygonal liver cells, an insufficiency produced by the action of bacterial or non-bacterial toxins or by prolonged anoxemia Very rarely an enormous overproduction of bilirubin can also produce this type of jaundice

Seldom is this type of jaundice, which is merely a functional cellular insufficiency maintained in the initial phase During this period it will be characterized by hyperbilirubinemia, an indirect Van den Bergh reaction, absence of bilirubin in the urine, increased bilirubin in the stools and the presence of urobilin in the urine Generally the pathologic process advances further and as a consequence, there is actual destruction of the hepatic polygonal cell, eventually leading to discontinuity and derangement of the bile canaliculi During this second stage, the Van den Bergh reaction will be direct and bilirubin will be found in the urine, as will be explained later

A Obstructive jaundice

The mechanism of complete obstructive jaundice in its early stages has recently been studied by Bumstead and the writer (12). After ligating the ductus choledochus, and cystic duct of dogs, we measured the blood bilirubin at different intervals and observed the Van den Bergh reaction The results were as follows first, there was an increase of the indirect Van den Bergh reaction, which appeared usually between the beginning and end of the second hour after obstruction Following this period the biphasic reaction appeared and usually lasted one to two hours Finally the direct reaction appeared 4 to 5 hours after obstruction, and remained as long as the obstruction persisted (figs 2 and 3) When obstruction was released, the sequence of the Van den Bergh reaction was reversed, i e, the direct reaction was replaced by the biphasic, then by the indirect and finally the reaction became negative (the dog has normally a negative Van den Bergh reaction) It was suggested that the first increase of the indirect type of reaction was due to a temporary reflex inhibition of the liver cell function due to ligation of the ducts This is comparable to the reflex anuria which may occur when the ureter is ligated It was also found

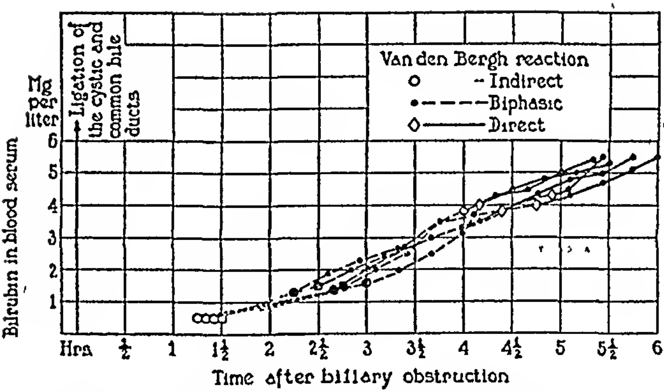


FIG 2 EXPERIMENTAL OBSTRUCTIVE JAUNDICE IN NEPHRECTOMISED DOGS CURVE OF BLOOD BILIRUBIN AND VAN DEN BERGH REACTION IN EARLY OBSTRUCTIVE JAUNDICE

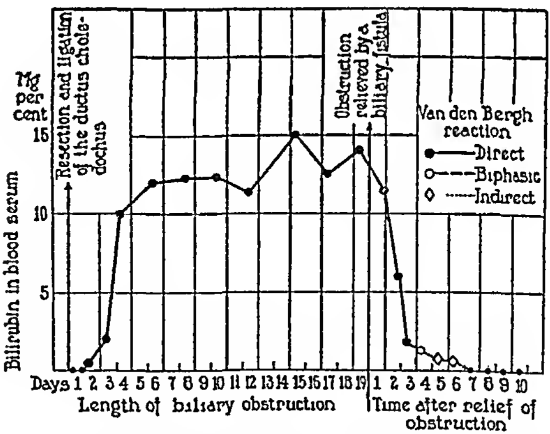


FIG 3 EXPERIMENTAL OBSTRUCTIVE JAUNDICE IN DOGS CURVE OF BLOOD BILIRUBIN DURING THE WHOLE PERIOD OF OBSTRUCTION TILL 7 DAYS AFTER RELIEF OF OBSTRUCTION BY A BILIARY FISTULA

that the direct reaction appears before any rupture of the bile capillaries is visible As the bile capillaries are dilated they extend between the liver cells as small distended pouches, the blind ends of these lying in contact with the capillary spaces Then diffusion of bile from these thin walled pouches into the perivascular spaces takes place, diffusion being favored by the mounting pressure within the bile ducts (as found by Bollmann, Sheard and Mann (24)) The latter was given as an explanation of the appearance of the direct Van den Bergh reaction These experimental studies have been confirmed by Mayo and Green (171), and they also have been frequently confirmed in this clinic, by the observation of numerous cases of obstructive jaundice, and especially those produced by gall stones where, when the jaundice begins to diminish the direct Van den Bergh reaction is changed into biphasic and then into indirect

The mechanism of complete obstructive jaundice of long standing is fairly well understood As shown by Eppinger (58) for the first time, and confirmed by Abramow and Samoilowicz (4) the bile canaliculi, in these cases, are distended and tortuous, and as their walls are frequently ruptured, the bile empties into the peri-vascular lymph spaces Associated with this, some necrosis of the liver cells accompanies obstructive jaundice (Ogata (207))

Obstructive jaundice can, therefore, be satisfactorily explained As the first period of hyperbilirubinemia associated with the indirect Van den Bergh reaction lasts only for a few hours, it can, for practical purposes, be discarded Obstructive jaundice may be characterized in the laboratory by hyperbilirubinemia with direct Van den Bergh reaction, the presence of bilirubin in the urine as soon as the renal threshold has been exceeded (about 2 mgm per cent of blood bilirubin), and the absence or scarcity of bile pigments in the stools Jaundice here appears more promptly than in the second group, probably because of the physico-chemical condition of the bilirubin in the blood As it remains free from adsorption by the serum proteins, it is more easily diffusible and thus stains the tissues in general, and the skin and mucosas in particular, more quickly than in the second group The degree of bilirubinemia will depend on the length of time and degree of obstruction, being more pronounced in cases of complete obstruction, and will follow the same course as that observed in experimental

obstructive jaundice (fig 3) Obstructive jaundice may be caused by the following pathologic conditions (1) An obstacle inside the lumen of the bile ducts, (2) alteration of the walls of the larger ducts, (3) a compression of the duct

Among the first group, the most common cause of jaundice is *cholelithiasis* Usually it is accompanied by all the symptoms of obstructive jaundice Sometimes, however, it gives only slight transient jaundice (Meulengracht (181)), in which case the direct Van den Bergh reaction can be of diagnostic importance According to Kehr (123) about 30 per cent of all gallstone cases and 75 per cent of common duct stone cases have a history of jaundice Takata (260) reports 15 cases of biliary colic examined during or shortly after the attack in every one of which an increase in the amount of bilirubin was found without the presence of visible jaundice

Parasites may produce obstructive jaundice Mertens (174) reports 48 cases in which *Ascaris lumbricoides*, entering the common bile duct from the duodenum, produced jaundice Recently, Labbé and Denoyelle (141) Fiessinger (68) and Panayotatou (209) have reported similar cases *Hydatids* (*Taenia echinococcus*) are a frequent cause of obstructive jaundice in cattle raising regions Castex, Romano and Beretervide (34) have related cases of hydatid cyst resembling the classic forms of obstructive jaundice

Jaundice due to hydatid cysts can be produced in the following ways (1) by rupture of the cysts into the lumina of bile ducts, (2) by mechanical compression of the bile ducts by a cyst developing in the interior portion of the liver (3) by complicated infections of the cyst or its surroundings (Trias Pujol (265)) *Faciola hepatica* (*Distomum hepaticum*), *Opisthorchis Sinensis* and *Opistohorchis noverca* have been found in the bile ducts (Rolleston and McNee (231))

The most common cause among the second group is *cholangitis* In its infective and suppurative form, it is usually associated with gallstones Kretz (136) describes under the name of *Icterus duodenalis* a type of jaundice produced by inflammatory swelling of the duodenal mucosa and subsequent inflammation of the end portion of the ductus choledochus Cruvelhier (43) states that scars produced by the cicatrization of duodenal ulcer can give place to a stenosis of the ductus choledochus Moynihan (197) reports 11 cases in which there was

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jaundice consequent to cicatrical contraction of the duodenal ulcer involving the papilla (see also Bickel (20)) Beingolea (18) reports a case of jaundice produced by duodenal diverticulum Primary tumours of the bile ducts, though rare, (Miller (189)) are among this group *Atresia* and *congenital stenosis of the bile ducts*, sometimes seen in infants, (Frensdorf (81) and Hallez, (96)) are also causes of obstructive jaundice

Among the third group there are in the first place, tumours compressing the bile ducts *Primary tumous of the liver* give rise to obstructive jaundice only when by their growth they compress large bile ducts (Counseller and McIndoe (41), Smith (254)). This is in accordance with the observation of McMaster and Rous (185), on the amount of biliary obstruction required to produce jaundice The bile ducts from three fourths of the liver substance in dogs and monkeys could be obstructed without any clinical evidence developing of pigment or cholate accumulation in the organism

Malignant tumours of the duodenum, especially of the papilla of Vater (Letulle (152)) are accompanied by jaundice In some cases of *tumours* of the *papilla of Vater*, Carnot (37) has observed intermittent jaundice before the development of a permanent jaundice *Malignant tumours involving the head of the pancreas* are frequent causes of jaundice (Fowler (78)). Millaré (190) finds that jaundice occurred in 82 cases out of 113 cases of tumours of the pancreas Whether *chronic pancreatitis* will or will not compress the common bile duct depends on the anatomical relation of the ductus choledochus to the head of the pancreas In 38 per cent of the cases the duct passes behind the head of the pancreas, and in these cases chronic pancreatitis need not compress the common bile duct In 62 per cent of the cases the common bile duct is imbedded in the head of the pancreas (Helley (101)) and in these cases jaundice usually occurs *Gummatous infiltrations* in and around the head of the pancreas cause rare cases of jaundice, *Pancreatic cysts* seldom press on the liver ducts and produce jaundice (McPhedran (186)) *Hemorrhagic pancreatitis* may be associated with jaundice *Large pancreatic calculi* in the ampulla of Vater or in the termination of Wirsung's duct, compressing the terminal part of the common bile duct, may give rise to jaundice (Gould (90), Kinnicut (127), Murray (200))

Enlarged glands of the hepatic pedicle can also produce obstructive jaundice, this enlargement being the consequence of intrahepatic inflammation, malignant disease, tuberculosis, syphilis, lymphadenoma and Hodgkin's disease Jean (117), Potosching (215), Hübsch (114) report cases of jaundice produced by tuberculous glands of the hepatic pedicle Pepper (211) reports a case of jaundice due to compression of the hepatic pedicle by an enlarged gland in a case of Hodgkin's disease Jaundice is a common complication of carcinoma of the stomach and Fenwick (65) reports the presence of jaundice in 13 7 per cent of cases

Aneurism of the abdominal aorta near the coeliac plexus may press on the common bile duct and so cause jaundice and dilatation of the gall bladder (Dickinson (52)) *Aneurism of the hepatic artery* may compress the bile ducts above the entrance of the cystic duct (Rolland (233)) *Aneurism of the superior mesenteric artery* near its origin from the aorta has been known to compress the bile duct and give rise to jaundice (Willson (280)) Scholl (248) reports a case of jaundice due to movable *kidney* *Hepataptosis* can also produce jaundice (Howell (113) Steele (256)) Poynder (216) reports that *ovarian tumours* can also be the cause of jaundice

Obstructive jaundice, especially when the obstruction is not complete, may last for a considerable length of time without endangering the life of the patient Wangensteen (274) reports a patient who lived for 3 years

B Non obstructive jaundice

a Non-obstructive jaundice followed by liver cell necrosis

The essential feature of this group is that jaundice starts as a consequence of an insufficiency of the polygonal liver cells giving place to a retention of the blood bilirubin Let us for convenience make a diagram of a portion of the liver (fig 4) Normally the bilirubin which diffuses from the blood capillaries into the perivascular spaces is taken up by the polygonal liver cells and excreted into the bile canaliculi and from thence to the intestine If this excretory function of the liver cells becomes damaged to a sufficient degree, or the damage being of lesser degree, if there is associated with it an increased production

of bilirubin, some of the pigment will be retained and a condition of hyperbilirubinemia results This bilirubin being adsorbed by the serum proteins is more or less protected from kidney excretion, and, to a certain extent, from diffusion through the blood capillaries in general. As a consequence the clinical symptom of jaundice will be reached only after the hyperbilirubinemia has lasted for some days An indirect Van den Bergh reaction associated with hyperbilirubinemia and absence of bilirubin in the urine will therefore be the characteristic of this phase of non-obstructive jaundice with necrosis But the pathological process seldom stops at this phase Generally, the damage of

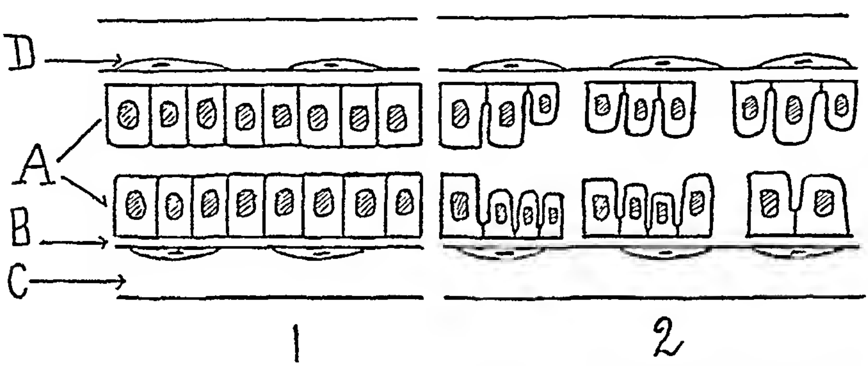

Fig 4. Diagram Representing a Section through the Liver Parenchyma

1 Normal liver *A*, polygonal liver cells, *B*, perivascular space, *C*, blood capillary, *D*, Kupffer cell.

2 Pathologic liver, showing polygonal liver cells at different stages of degeneration.

the liver cell increases, and, as a consequence, some of the cells reach the final state of destruction The continuity of the bile canaliculi having been destroyed, it is obvious that some of the bile will reach the perivascular spaces and diffuse into the blood capillaries The above represents the second stage of this jaundice group, where the Van den Bergh reaction is direct, jaundice is more intense, and bilirubin is found in the urine If the body overcomes the pathological process, the liver cells regenerate, and the discontinuity of the bile canaliculi having disappeared, the Van den Bergh reaction will become indirect, remaining above the normal limits until the cells have recovered their normal function The Van den Bergh reaction in the average or severe cases of this type of non-obstructive jaundice behaves

in the same way as it does in obstructive jaundice However, there is this important difference that here the indirect Van den Bergh reaction lasts a longer time and changes into the direct type only as a consequence of cellular destruction It is in the study of this type of jaundice that Van den Bergh's contribution has been of the utmost value, not only for differential diagnosis but especially for prognosis If benign cases of this group are accompanied by an indirect Van den Bergh reaction, the transformation of the Van den Bergh reaction into the direct type will be the consequence of a severe cellular damage leading to necrosis of the polygonal cell The greater the severity of the liver cell damage, the greater will be the bilirubinema If the inflammatory process has subsequently produced the obstruction of bile capillaries or bile ducts (cholangitis) there will also be more or less decoloration of the stools However, its distinctive feature and progress will remain invariable, as above outlined

Two main groups belong to this type of jaundice (I) infectious jaundice, (II) toxic jaundice

Infectious jaundice

The modern conceptions of the pathogenesis of infectious jaundice have been based on the researches of Chauffard, Widal and his collaborators, and it required a long time to relinquish the old classical theories based on Vichow's observations, namely, that this kind of jaundice was produced by occlusion of the bile ducts, and that the infection was of intestinal origin, being transmitted to the liver via the bile ducts It is of interest to recall that Chauffard (48) was the first to point to the insufficiency of the liver in catarrhal jaundice, this fact resulting from his experiments on alimentary glycosuria and intermittent elimination of methylene blue Whether jaundice appears as a complication in the course of a general infection or whether it is the main symptom of the malady, the course of events is the same, infectious hepatitis, damage of the liver cell, with impairment of its functions It is not until some time later, as the infection progresses, that a cholangitis develops, and the classic bile thrombi may be seen within the lumen of the bile capillaries Infectious jaundice can be divided into two groups, primary and secondary But either one or the other form will follow the same evolution

Sometimes the infection is of a benign type, and liver damage is recognized only by the presence of hyperbilirubinemia with an indirect Van den Bergh reaction, urobilinuria, absence of bilirubin in the urine and subicterus Generally the infection produces a destruction of some hepatic cells, and subsequent cholangitis, and the jaundice will become more evident with the development of a direct Van den Bergh reaction Chauffard says "en matière d'ictère infectieux, depuis l'ictère catarrhal le plus simple jusqu'à l'ictère grave le plus rapidement mortel, tous les intermediaires existent" The nature of the organism, the intensity and duration of the infection, the localization and variety of the hepatic lesions are the factors which govern the degree and character of bilirubinemia, and determine the clinical course of the disease

Primary infectious jaundice Under this group are considered those cases where the initial septicemia has attacked the liver primarily

Spirochetal jaundice, not infrequent in the United States (Sailer (242), Hayman (100)), is a very well known clinical entity since the discovery of its causal agent (*Spirocheta ictero-hemorrhagica*, by Inada and Ido) Jaundice starts 4 or 5 days after the onset of the malady, and reaches its maximal intensity 2 or 3 days later There have been no reports of the degree and quality of bilirubinemia during the first days and the only available figures are those found when jaundice is an obvious symptom

Yellow fever Generally jaundice makes its appearance on the third day of the malady but at times is recognized on the second day, or even may not be definitely present during life, or recognized only shortly before death The Van den Bergh reaction according to Klotz and Simpson (132) gives a high indirect type when performed one day before the appearance of jaundice Afterwards it becomes direct

Catarrhal jaundice A mild infectious jaundice with varied etiology, it is a common disease In numerous cases the presence of *Bacillus paratyphosus* in the blood has been reported (S Coste, Boyer and Montel (39, 40), Sacquepée (239), Frankel (80) Sarrailé (240) Cantacuzene (32)) More rarely *Bacillus typhosus* (Savy and Delachanal (241)) and *Bacillus coli* (Widal, Lemierre and Bénard (276)) have been isolated Unfortunately, in the vast majority of cases in this country, it has not been possible to isolate the germ which is the underlying cause of catarrhal jaundice

Secondary infectious jaundice Numerous infections are complicated by jaundice *Pneumonia* is frequently accompanied with hyperbilirubinemia and clinical jaundice There has been some discussion about the origin of jaundice in pneumonia Banti (10) thought that it was of hemolytic nature and in support of this theory Pollack (213), Herzfeld and Steiger (105) reported the presence of bilirubin in the sputum But as Feigl and Querner (64) pointed out, the hepatic nature of this sort of jaundice is now clear To the initial infectious hepatitis, sometimes a condition of anoxemia is added, which can precipitate or increase the jaundice Lundsgaard (157) observed a decrease in the content of the oxygen of the capillary blood in 10 to 20 per cent of patients with lobar pneumonia Hastings and coworkers (99) in 10 cases of pneumonia, found 8 in which on one or more occasions there was an arterial saturation of oxygen below 90 per cent In six cases the arterial saturation was below 85 per cent, a level of arterial saturation at which symptoms of mountain sickness may begin in normal individuals who are transferred to high altitudes (Bancroft et al (11), Monge (194)) Binger (22) in 130 patients with lobar pneumonia finds that 50 per cent of them show an oxygen saturation between 80 to 89 per cent Radvig (220) observed in a series of nine patients with lobar pneumonia, one case with direct reaction, two with biphasic reaction and four with high indirect reaction Schiff (246) reports clinical jaundice in 21 out of 826 cases of lobar pneumonia, of which only eight died, and concludes that jaundice is not of serious prognostic significance Although the presence of hyperbilirubinemia with indirect Van den Bergh reaction is of no serious prognostic significance, the writer is of the opinion that a direct Van den Bergh reaction in pneumonia must be seriously considered as it indicates an advanced hepatitis The prognosis is particularly serious when jaundice occurs during pneumonia in children

Jaundice in syphilis Early jaundice during the secondary manifestations of syphilis has often been reported, and recently O'Leary, Greene and Rowntree (208) mention one case in which the bilirubinemia, when the jaundice was already established, reached 7 9 mgm per cent, the reaction being of the direct type Late jaundice in untreated syphilis is ordinarily a result of interference with the outflow of bile by a gumma of the liver or scarring of the liver Jaundice can

follow an initial injection of arsphenamine due to the Herxheimer reaction, which is characterized by an exaggeration of the local inflammatory process

Many other infections may produce jaundice as a complication, its pathogenesis being the same as in all cases of infectious jaundice, e g, streptococcus infections (Abrami, Richet and Monod (3), scarlet fever (Meurisse (175), Izard (115)), gonoccous infectious (Raynaud, Montpellier and Boutin (222)), appendicitis (Caplesco (33)), infectious mononucleosis (Mason (169)), influenza (Crawford (42))

To give a long table indicating the degree of bilirubinemia found in the clinic in these different forms of jaundice would be superfluous When the infection is of mild nature and produces only a moderate hepatitis with slight cellular insufficiency, there will be a moderate hyperbilirubinemia, with indirect Van den Bergh reaction Clinically there will be no jaundice or a slight degree of jaundice in the mucosas, especially the conjunctiva If the infection has been more intense and as a consequence some hepatic cells have been destroyed, thus breaking the continuity of the bile channels, the jaundice will become obvious, the hyperbilirubinemia will increase, and the Van den Bergh reaction will become direct In infectious jaundice as well as in toxic jaundice all degrees of bilirubinemia are observed

Toxic jaundice

Intoxications as well as infections produce in the liver a similar series of effects resulting in the degeneration and death of the hepatic cells When the intoxication is slight the liver damage may be of so mild a nature that no clinical symptoms of jaundice are found The liver insufficiency will be recognized only after the performance of functional tests Hyperbilirubinemia with indirect Van den Bergh reaction will be generally present When the intoxication is of more severe type, the cellular degeneration produces the destruction of more or less extended areas of liver parenchyma Jaundice, hyperbilirubinemia with direct Van den Bergh reaction will be present, the mechanism of its production being the same is in infectious jaundice Granting the same degree of cellular damage, the degree of hyperbilirubinemia will depend upon whether the toxic substances act on the liver cell alone or whether they produce at the same time an increased

destruction of red blood cells (hemolytic poisons) As non-obstructive jaundice is a function of two factors, e g , the efficiency of the liver cell and the degree of bilirubinemia, it is obvious that hyperbilirubinemia will be found if to a liver cell, slightly insufficient, but still able to excrete the bilirubin from the blood when present in normal amounts, is associated an increased red cell destruction

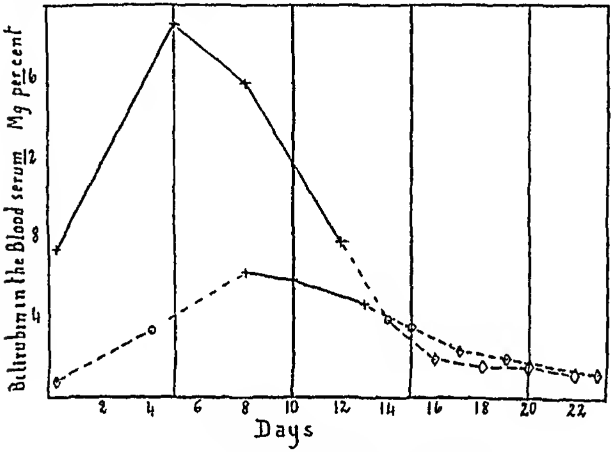

FIG 5 BILIRUBINEMIA IN ARSPHENAMINE JAUNDICE

1 Twenty days after treatment (Received at the Clinic with symptoms of jaundice)
2 Ten days after treatment
◇ ———— Indirect Van den Bergh reaction
○ = = — — Biphasic reaction
+ ———— Direct reaction

Arsphenamine jaundice Since the introduction of salvarsan and its allied compounds in the treatment of syphilis, varying degree of hepatitis have resulted from their use, which sometimes end in death This is due to the poisonous effect of the drug or of its decomposition products Isolated opinions denying the toxicity of arsphenamin (Millian (191)) are unfounded and have been contradicted by unfortunate experiences, where the death of the patient followed continua-

tion of salvarsan injections, after jaundice had appeared as a complication of treatment (Ravaut (221)) Jaundice can occur a few days after treatment (early jaundice) or several weeks after the end of a course of treatment (late jaundice) (Report of Salvarsan Committee of the Medical Research Council (173)) The earliest jaundice after salvarsan treatment has been reported by Stumpke and Bruckmann (259), who found jaundice two hours after the injection Generally, however, it is from 10 to 20 days after treatment that jaundice becomes manifest.

Early jaundice is usually of a mild evanescent character and seldom severe and persistent On the other hand, late jaundice is more serious and prolonged, and may sometimes be an expression of acute yellow atrophy of the liver Gerard (83), from 370 cases of syphilis treated with arsphenamine, finds that 281 did not show hyperbilirubinemia at any time However, there was hyperbilirubinemia in 89 cases, i e, in 24 per cent of the cases Friedeman (82) states that 35 per cent of his cases showed hyperbilirubinemia

Martin and the writer,[3] studying cases of arsphenamine jaundice have found that the evolution of bilirubinemia and the Van den Bergh reaction follow the same steps as those already described as characteristic of this group of jaundice (fig 5) The first phase of hyperbilirubinemia with indirect Van den Bergh reaction can be recognized only when doing bilirubin determinations continuously and before any clinical signs of jaundice are noticed, the second and third phases (i e, biphasic and direct Van den Bergh reactions) are found as soon as clinical jaundice is present The last phase of hyperbilirubinemia with indirect reaction lasts for many days, showing evidence of the slow recovery from a complete liver efficiency

Patients with high bilirubinemia, indicating, of course, damage to the liver, should be protected from further damage by withholding salvarsan (Dixon, Campbell and Hanna (53)) The Van den Bergh reaction and bilirubin determinations must be continuously performed, not only during arsphenamine treatment, but especially before the use of the drug When arsphenamine is administered to a patient having a bilirubinemia of about 5 mgm per liter, the use of the drug must be suspended as soon as this bilirubinemia begins to increase

[3] Unpublished observations

The toxic effect of *chloroform* on the liver cells is very well known, as it is frequently employed for experimental purposes Drury and Rous (54) found that after prolonged chloroform anesthesia there was an acute suppression of bile, as evidenced by the secretion of "white bile" from which bilirubin, cholesterol, and bile salts were absent This bile suppression was found to be due to a disturbance of the excretory power of the liver cells

Carbon tetrachloride as a specific poison of the liver cells has been reported by Lamson and his associates (142–145) The toxic effect of *phosphorous* on the liver cell is very well known Other drugs have been mentioned as capable of producing toxic jaundice, e g , atophan (Klinkert (131)), biloptin or diiodoatophan (Schwarz (250)), luminal (Neber (201)), acetylene tetrachloride (Schibler (245))

During the great war *picric acid* was used to simulate jaundice Merklen (176), Brulé, Javillier and Baeckeroot (30) were able to demonstrate that picric acid when taken during prolonged periods can produce a toxic hepatitis, and as a consequence, a true jaundice can result

Roentgen ray irradiations can also produce toxic jaundice Cameron and Flecher (31) relate two cases, one of carcinoma of the pancreas without liver involvement, and the other of carcinoma of the pylorus, where two days after exposure to Roentgen rays, there was a rise in the bilirubinemia Case and Warthin (36) also mention the occurrence of hepatic lesions in patients treated by intensive deep Roentgen radiations

The action of *ultraviolet rays* has been studied by Pennetti (210) He exposed dogs to the action of ultraviolet rays and determined the number of red blood cells, hemoglobin and bilirubinemia He found a small increase of red blood cells and hemoglobin after the first few days, due to the stimulating action of these rays upon the hemopoietic organs and bone marrow in particular The bilirubinemia remained constant After this came a second period with diminution of red blood cells and hemoglobin, accompanied by an increase of bilirubinemia, which disappeared rapidly after suspension of treatment

Mercury has a more selective action upon the kidneys, but cases have been reported where it also produced hepatic lesions resulting in jaundice (Fiessinger (69), and Letulle, Le Noir, Oettinger (153))

In this clinic the writer has observed a case of mercury intoxication where there was a biphasic reaction with a bilirubinemia of 1 5 mgm. per cent

Tetrachlorethane (employed in the fabrication of artificial pearls) when absorbed in the vapor state by inhalation, can produce jaundice (Wilcox (279), Fiessinger, Brodin and Wolf (70)) *Trinitrotoluene*, used during the war as an explosive in shells, and dinitrobenzol, are also responsible for the production of jaundice (Spilsbury, Turnbull and Stewart (255))

Among the foodstuffs capable of producing toxic jaundice, mention must be made of jaundice produced by mussels (Fiessinger and Ravina (71)), and poisonous mushrooms

Lead, toluylenediamine, and acetic acid all produce jaundice by a double mechanism To their toxic effect upon the liver cells has to be added their hemolytic action on the red blood cells As a consequence, jaundice will appear as an early symptom These cases of toxic jaundice are extremely interesting as they throw light on the pathogenesis of many cases grouped under the name of "hemolytic jaundice" Let us take acetic acid (Kaznelson (121), Landau (146)), or intoxication by lead (Lewin (155)), since both have the same form of action When one of these toxins is administered in small doses, there is first an increased destruction of red blood cells, soon followed by a slight insufficiency of the liver cells with concomitant hyperbilirubinemia Here the hyperbilirubinemia is produced by two combined factors, either of which, when separated, would not alone be able to produce bilirubin retention The Van den Bergh reaction in this case is indirect If the amount of toxin is increased, there is produced a jaundice similar to an ordinary catarrhal jaundice In both cases injury of the liver can progress to the so-called yellow atrophy Toluylenediamine jaundice has an interest because it has been widely used for experimental purposes, and its pathogenesis has been the subject of many discussions Formerly considered as a true hemolytic jaundice, today its hepatic nature is undoubted, as confirmed by Eitel's (56), and Yuasa's (287) recent investigations The nature of the jaundice produced by *phenylhydrazine* (a drug used in the treatment of polycythemia vera) has been recently investigated in Aschoff's laboratory by Alcobé (2) and Abeloff and Hummel (1) Unfortunately their

contradictory experiments cannot be regarded as conclusive and the solution of this problem requires further research. It is probable, though not yet proved, that phenylhydrazine acts in the same way as toluylenediamine does, i.e., by impairing the excretory function of the liver cells and at the same time, by producing, due to its hemolytic properties a sudden increase in the bilirubin formation.

Cardiac jaundice. The cause of jaundice in circulatory failure has been from time to time the source of discussion, owing to the difference of opinion as to whether the hepatic lesion was due to a circulatory disturbance or whether to a toxic factor, bacterial or non-bacterial. Oertel (206) came to the conclusion that jaundice was not due to an hepatitis, but was most probably due to a mechanical cause in the form of chronic stasis. Mallory (165), on the other hand, held that the disappearance of liver cells in chronic passive congestion was the result of bacterial necrosis. Bolton (25), studying experimental venous passive congestion of the liver, came to the conclusion that the mechanical factor of stasis was the only cause in these cases. Meakins (172) gives as a cause of stasis the slowing of the circulation, aggravated by anoxic-anoxemia. Fischberg (76) explains this jaundice by the combination of two factors: (1) injury to the liver cells by chronic passive congestion and, (2) increased destruction of red cells. Eppinger (59) considers that the chief source of hyperbilirubinemia is the multiple hemorrhagic infarcts which occur so readily in the congested lungs and speaks of the similarity of the histologic picture of the spleen in chronic passive congestion and hemolytic jaundice.

It is now generally agreed that chronic passive congestion which severely injures and often destroys many liver cells about the efferent veins of each lobule, is the fundamental cause of the hyperbilirubinemia present in cardiac failure. Two theories have been formulated to explain its production: (1) that the cells are damaged by pressure from the dammed-back blood, and, (2) that they are damaged by the deficient supply of oxygen. Rich (229), in collaboration with Bumstead, observed that in pernicious and secondary anemias as well as in experimentally produced anemias, the cells about the efferent veins of each liver lobule may be damaged in a manner often indistinguishable from that accompanying chronic passive congestion, and he put forward the opinion that the damage to the liver cells in chronic passive

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serum and concluded that this bilirubinemia was caused by the action of anoxemia. It is well known, since Lamson's observations, that carbon tetrachloride alone produces bilirubinemia from 24 to 48 hours after the administration of the drug. Rich and the writer (15) have kept dogs under reduced oxygen tension (from 6 to 8 per cent oxygen content) for a period of 8 to 10 days. At the end of this period, bilirubin was injected intravenously and its concentration measured in the blood of these animals at definite intervals thereafter. The curves obtained were compared to those found under normal conditions. In anoxemic dogs there was an obvious decrease in the rate of bilirubin excretion (fig. 6) thus showing conclusively that the liver cells are very susceptible to anoxemia.

The reason for the frequency, evolution and appearance of jaundice in cardiac disease becomes thus quite clear. Anoxemia must be present over a long period in order to produce sufficient liver damage. Clinical experience obviously confirms this view, as hyperbilirubinemia, when occurring in heart disease, is present only in the chronic forms. The greater frequency of jaundice in mitral disease is also easily comprehensible. The anoxemic condition of the liver caused by chronic passive congestion, produces an insufficiency of the liver cells and gives rise to a hyperbilirubinemia with an indirect Van den Bergh reaction. This state of latent jaundice is often masked by the difficulty in recognizing the colour of the skin due to the accompanying cyanosis. When cardiac failure is complicated with infarcts of the lungs, jaundice is specially apt to occur (Eppinger (60), Libman (156), Rich and Resnik (229) and Keefer and Resnik (126)). In this condition the pathogenesis is explained on the same basis, for the existing anoxemia has been increased, the damage to the liver cells is suddenly exaggerated, and the latent jaundice is then transformed into clinical jaundice. The Van den Bergh reaction becomes either biphasic or direct, depending on the proportion of liver cell destruction.

Cirrhosis of the liver. The degree of hyperbilirubinemia in cirrhosis of the liver depends on the extent of the chronic inflammation produced by the causal agent (toxins, infections, parasites), and the extension and distribution of the fibrous reaction. In portal cirrhosis, either of the Laennec or the hypertrophic type, the insufficiency of the liver cells, at least at the early stages, can ordinarily be discovered only

by studying the ability of the liver to excrete bilirubin intravenously injected (von Bergman (17)) Occasionally, there is found in portal cirrhosis, a slight degree of hyperbilirubinemia (Gilbert, Herscher and Posternack (86), Diamond (50)), and the Van den Bergh reaction is always indirect Clinically, jaundice is generally absent and appears only during the late stages of the disease, when there is increased cell destruction or obstruction of many bile canaliculi by the fibrous tissue reaction, in which case the Van den Bergh reaction becomes biphasic or direct Green, McVicar, Snell and Rowntree (95), in eleven cases of the Laennec type of cirrhosis, found three cases showing the direct Van den Bergh reactions (from 2 9 to 1 6 mgm per cent) In cases of biliary cirrhosis, hyperbilirubinemia is more marked, jaundice is a constant symptom, and the Van den Bergh reaction is direct

Jaundice in pregnancy

The function of the liver in pregnancy has attracted considerable attention, as pathological alterations of this organ are frequently found in complicated pregnancy (eclampsia, hyperemesis gravidarum) Tarnier and Blot speak of an hepatic insufficiency present in pregnancy Hofbauer (110) maintains that as a consequence of the compression of the gravid uterus there is a venous stagnation of the liver which may produce definite alterations of the parenchyma (fatty degeneration of the liver cells, deficiency of the stored glycogen) He calls this state of liver insufficiency, "Schwangerschaftsleber" Westphal (275) speaks of an increased excitability of the vagus which would produce a spasm of the bile ducts and a consequent bile stagnation These theoretical considerations have not yet found positive evidence Although most of the authors (Mikeladse (192), Eufinger and Bader (63), Schulntz (247), Breda (27), Schmidt (243) report a slight hyperbilirubinemia (not over 0 7 mgm per cent) in normal pregnancy, which falls to normal after delivery, the true nature of this hyperbilirubinemia has not yet been clearly established It would be of interest to test the bilirubin excretory power of the liver of normal pregnant women with the intravenous injection of bilirubin since with this test, slight liver insufficiencies can be detected But if hyperbilirubinemia has no importance in normal pregnancy, its presence in diseases of pregnancy is certainly of great importance Heynemann (106) advised

that all cases of pregnancy having over 1 mgm per cent of bilirubin in the blood serum be observed carefully Hyperemesis gravidarum and eclampsia are often accompanied by jaundice, and Eufinger and Bader (63) in 20 cases of hyperemesis found 8 cases with direct Van den Bergh reaction, and in 15 cases of eclampsia observed 8 cases with direct Van den Bergh reaction All the authors agree upon the following conclusions The estimation of bilirubin in the blood serum of these patients is of great value in prognosis, since there is a parallelism between the gravity of the symptoms and the degree of bilirubinemia

b True non-obstructive jaundice

The nature of true non-obstructive jaundice has been and still is the subject of much controversy Catalogued by the majority of authors under the title of "hemolytic jaundice," it was considered as due essentially to an increased red cell destruction, and overactivity of the centers where their destruction takes place It seems that these investigators, impressed only by one of the factors which enter into the production of jaundice overlooked the other factor, i e, the efficiency of the liver cell in excreting bilirubin

Rich[4] has recently pointed out that to maintain a persistent non-obstructive jaundice a combination of two factors are almost always required (1) an increased bilirubin production, and, (2) an insufficiency of the liver cells The question arises "what may cause insufficiency of the liver cells?" The experiments of Rich and the writer, previously cited, demonstrated that by the sole action of prolonged anoxemia in dogs the following phenomena resulted (1) a diminution of the ability of the liver to excrete bilirubin injected intravenously, and (2), microscopically (in dogs and guinea pigs), the production of lesions of the liver analogous to those found in pernicious anemia, hemolytic jaundice, sickle cell anemia and anemia experimentally produced in dogs by long continued hemorrhages These experiments show that the mechanism of injury to the liver cells in this type of jaundice is produced by the combination of two factors (1) The production simultaneously of hyperbilirubinemia and anemia, due to prolonged and increased destruction of erythrocytes, (2) a chronic

[4] To be published

state of anoxemia due to the anemia which injures the liver cell and diminishes its bilirubin excretory function Hyperbilirubinemia plus inefficient function of the liver cell will produce jaundice It is true that the injury resulting from this mild state of anoxemia is not sufficient to produce by itself a bilirubin retention If the amount of bilirubin elaborated by the reticulo-endothelial system does not exceed the normal limits (anemia by hemorrhage) the liver cell will still be able to excrete the pigment As soon, however, as the bilirubin production exceeds the normal limits, the liver cell will be unable to dispose of the excess and permanent hyperbilirubinemia and jaundice will follow

Malaria

Since the malarial parasites live within the red blood cells, every erythrocyte harboring the Plasmodium will be destroyed As a consequence, every attack of fever diminishes the total number of red blood cells from 5 to 10 per cent, and anemia is the immediate consequence The spleen becomes enlarged, since this organ plays an important rôle in the catabolism of destroyed erythrocytes Chauffard (46) has described a syndrome "hepato-splénique" in cases of acute malaria In these cases, splenomegaly is the first symptom to appear After treatment, the spleen reverts to its normal size, while the liver becomes congested and increases its volume

The degree of bilirubinemia in malaria depends on the clinical type of the disease, and its duration The accompanying jaundice is related to the degree of anemia, that is, the greater the anemia, the deeper the jaundice

In acute malaria there is transient hyperbilirubinemia but seldom jaundice During the attack of fever the bilirubinemia rises above its normal value Schachsuvarly (243), Russo and Serbinoff (238) find hyperbilirubinemia which reaches as high as 6 mgm per cent Kingsburg (128) in 150 cases of malaria finds that the bilirubinemia reaches an average of 0 74 mgm per cent in quartan malaria, 1 74 mgm per cent in tertian malaria, and 2 mgm per cent in tropical malaria Ross (236), from 30 cases of tertian malaria, finds hyperbilirubinemia in 29 In all of these cases the Van den Bergh reaction was of the indirect type While Arellano (9) and Kingsburg (128)

find a relation between the size of the spleen and hyperbilirubinemia, Schachsuvarly (243) denies this relationship

Special mention must be made of the behaviour of "malaria inoculata," the use of which is increasing since its introduction by Wagner von Jauregg as a therapeutic procedure in the treatment of neurosyphilis In spontaneous malaria, all authors agree as to the presence of hyperbilirubinemia with a constant indirect Van den Bergh reaction A more or less severe liver damage is often produced in malaria inoculata, as manifested by the presence of clinical jaundice with the direct Van den Bergh reaction O'Leary and his associates (208) report six cases of malaria inoculata, all showing direct Van den Bergh reactions and a bilirubinemia of from 3 mgm to 23 mgm per cent In this clinic, out of eleven cases of malaria inoculata, there was one giving a direct reaction and bilirubinemia of 6 01 mgm per cent, five giving biphasic reactions and bilirubinemia of from 2 mgm to 3 57 mgm per cent the remaining five cases behaved as spontaneous malaria (slight hyperbilirubinemia with indirect Van den Bergh) It is not at present clear just why more severe liver damage occurs in malaria inoculata than in spontaneous malaria

Blackwater fever

The considerable erythrocyte destruction occurring in this disease can produce a transient and early hyperbilirubinemia, due solely to bilirubin overproduction and inability of the normal liver cell to get rid of this excess bilirubinemia The jaundice present in this disease, however, is generally due to severe liver damage as Ross has shown Ross (236) finds the presence of a hyperbilirubinemia with the indirect type of Van den Bergh reaction when extremely mild hemoglobinuria develops When the jaundice is manifest, and hemoglobinuria severe, the Van den Bergh reaction becomes positive

Carrion's disease (Oroya fever)

This disease, caused by a blood parasite, Bartonella bacilliformis, and characterized essentially by prolonged fever and severe anemia, with a blood picture of intense regeneration, is confined to the occupants of the valleys of Peru, and presents an extremely interesting clinical picture Few other pathological entities produce so severe a

state of anoxemia due to the anemia which injures the liver cell and diminishes its bilirubin excretory function Hyperbilirubinemia plus inefficient function of the liver cell will produce jaundice It is true that the injury resulting from this mild state of anoxemia is not sufficient to produce by itself a bilirubin retention If the amount of bilirubin elaborated by the reticulo-endothelial system does not exceed the normal limits (anemia by hemorrhage) the liver cell will still be able to excrete the pigment As soon, however, as the bilirubin production exceeds the normal limits, the liver cell will be unable to dispose of the excess and permanent hyperbilirubinemia and jaundice will follow

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destruction of erythrocytes (Arce[5]) During the first period of the disease, called by Weiss (281) the "hematic phase," the germ affects predominantly the circulating erythrocytes When the second period or "hystioid phase" is reached, the germ is mainly localized in the cells of the reticulo-endothelial system In Carrion's disease, as in malaria, hyperbilirubinemia and jaundice run parallel to the degree of anemia The Van den Bergh reaction is always of the indirect type (Guzman-Barron, A (94))

Icterus neonatorum

Among the many varieties of jaundice, icterus neonatorum has occupied a peculiar place for many years Though its clinical character, its frequent occurrence and its benign course are very well known, its pathogenesis has caused considerable discussion The question of its hepatic or hemolytic origin has been much debated Unanimity of opinion, among pediatricians, has not yet been reached From the considerable literature devoted to the subject one gathers the following facts

Hyperbilirubinemia is normally present in the new born and is even present during intrauterine life, since it is found that the bilirubin content of the blood of the cord is higher than that in the blood of the arm of the infant (Hirsch (109), Yllpo (288), Schiff and Farber (252)) The Van den Bergh reaction is always indirect whether the blood be taken from the umbilical cord or from the arm (Klemperer (129), Knopfelmacher and Kohn (133), Grulu and Mebane (92), Lepehne 149)) The amount of bilirubin increases after birth, reaches its maximum between the fifth and seventh day and then subsides (Hallez (97), Mitchell (193)) This is explained in the following manner

There is normally a polycythemia in the newborn (Lereboullet (150), Ziegelroth (290)), and an increased number of young immature nucleated red blood cells (Greil (88), Goldbloom-Gottlieb (89)), due to a chronic state of anoxemia during the intrauterine life (Ziegelroth (290)). After birth these cells are destroyed in excess as shown by the hemoglobin determinations and red blood cell counts (Williamson (283)) This red cell destruction may sometimes be accelerated either by the presence of hemolysins from the serum of the mother (observed

[5] Arce J Clinical Lectures

by Mitchell (193) and Lenart (147) though Goldbloom and Gottlieb (89) have not been able to confirm it), or by a marked increase in the fragility of the red corpuscles (Goldbloom and Gottlieb (89)) Jaundice is most frequent in premature, under developed infants (Lereboullet (150))

There is a functional insufficiency of the liver of the newborn due to a functional immaturity of the liver (Heynemann (107), Illpo (289)), which in some cases has been detected by using liver function tests unrelated to the bilirubin excretory power, e g , levulose test, Widal test

There are, therefore, in icterus neonatorum, the two factors which Rich regards as necessary to the production of true non-obstructive jaundice, namely, increased red cell destruction and insufficient liver cell function

Pernicious anemia

Scheel (244) was the first to show the presence of hyperbilirubinemia in pernicious anemia, but until Van den Bergh's (269) studies, no quantitative determinations were made Van den Bergh reported an increase of bilirubinemia in pernicious anemia from four to eight times above the normal values Numerous investigators have subsequently reported the presence of hyperbilirubinemia in pernicious anemia (Eppinger (60), Botzian (26), Robertson (232)) Leaving out of account the etiology of the disease, which is still unknown, pernicious anemia belongs to the group of anemias with red cell destruction This increased red cell destruction is favoured by the extrusion into the general circulation of young immature erythrocytes condemmed to early destruction by the reticulo-endothelial system There are, therefore, present in pernicious anemia the two factors necessary for the production of permanent bilirubin retention liver cell insufficiency as a consequence of longstanding anemia and over-production of bilirubin

This liver insufficiency in pernicious anemia has been indicated in studies by Harrop and the writer, (13), who have measured, in pernicious anemia patients, the bilirubin excretory function of the liver While normally the liver excretes within two to four hours the bilirubin injected intravenously (1 mgm bilirubin per kilogram of body weight), patients with pernicious anemia and *normal* bilirubinemia show a marked retention of the injected pigment (fig 7)

hemolysin becomes active through the influence of the complement normally present in the blood, and hemolysis ensues Kohler and Obermayer (135) observed a patient whose red blood cells fell 690,000 per cubic millimeter during an attack Montagnani (195) reports a case where there was a loss of two million red cells per cubic millimeter Jones (119), studying the bilirubin concentration in the blood and duodenal contents found, first a transient state of hyperbilirubinemia which reached its maximum 45 minutes after the attack, from this point the bilirubin gradually returned to normal, while the bilirubin of the duodenal content increased correspondingly

Following the more severe attacks of hemoglobinuria, a little icteric staining of the sclerae and skin is perceptible for a few days (Mackenzie (166), Barta, and Gorog (16))

Ectopic pregnancy, extravasation of blood

Whenever there is a local hemorrhage, the hemoglobin of the extravasated blood is changed into bilirubin, but the appearance of jaundice is extremely rare, as the excretory power of the liver cells is sufficient to prevent its appearance Dick (51) reported three cases of ruptured *ectopic* pregnancy with severe intraperitoneal hemorrhage, jaundice of the skin and conjunctiva and no bile in the urine Norris (205) reports two patients with ruptured ectopic pregnancies and jaundice, and states that the presence of jaundice is of great importance, and may frequently be the symptom which determines the differential diagnosis, but Horowitz and Kuttner (112) have recently denied the presence of jaundice in ectopic pregnancy, since, in fifteen cases, they did not find increased bilirubinemia

Congenital and acquired hemolytic jaundice was described for the first time by Minkowski (188), and was characterized in its essential features by Chauffard (44, 47) and by Widal and his associates (277) Hemolytic jaundice, as is well known, is characterized by hyperbilirubinemia with indirect Van den Bergh reaction, absence of bile in the urine, coloured stools, lowering of the osmotic resistance of the red blood cells against hypotonic solutions of sodium chloride, a considerable enlargement of the spleen, chronic anemia and morphologic alterations of the red blood cells Jaundice is such a dominant symptom that Chauffard has described these patients epigrammatically

as "plus ictériques que malades" The bilirubinemia is variable Botzian (26) finds figures fluctuating from 2 to 9 15 mgm per cent Kaznelson (122) reports, in one case, a bilirubinemia of 7 25 mgm per cent Schiff (246) finds from 2 5 to 7 5 mgm per cent In this clinic the values fluctuate between 2 mgm and 9 94 mgm per cent The last figure seems to be the highest bilirubinemia found in hemolytic jaundice The Van den Bergh reaction in this case was "delayed biphasic," i e, the colour reaction appeared thirty seconds after the addition of the diazo-reagent, reaching its maximum intensity several minutes later, but no bile was found in the urine It has been said that a solution of bilirubin added to normal serum gives an indirect reaction, until a certain concentration is reached (16 mgm per cent) beyond which the reaction becomes direct It is therefore, possible, though probably extremely rare, to observe cases of hemolytic jaundice giving biphasic Van den Bergh reactions If the amount of bilirubin exceeds the saturation point, or, the bilirubinemia being not so high, if the concentration of serum protein is lowered, theoretically a change in the Van den Bergh reaction may appear

The disappearance of jaundice observed in cases of congenital hemolytic jaundice after splenectomy, has been confirmed through bilirubin determinations before and after splenectomy by several investigators (Rich and Rienhoff (228), Schiff (246)) Sometimes, after splenectomy, there is a change in the Van den Bergh reaction A case of this nature was observed in this clinic A patient with hemolytic jaundice (indirect Van den Bergh reaction, bilirubinemia, 8 34 mgm per cent) was splenectomized The day following the splenectomy, the Van den Bergh reaction became biphasic, and the bilirubinemia dropped to 3 76 mgm per cent Some days later the Van den Bergh reaction became indirect with a bilirubinemia of 1 mgm per cent That the spleen takes a considerable part in the overproduction of bilirubin has been demonstrated by Kaznelson (122), Eppinger (60) and others, who found more bilirubin in the splenic vein than in the peripheral circulation

Although the excellent results obtained by splenectomy in cases of congenital hemolytic jaundice seem to favor Minkowski's first observation that this is primarily a disease of the spleen, the persistence, in some cases, of the diminished osmotic resistance of the red blood cells after splenectomy complicates this interpretation

In *acquired hemolytic jaundice* splenomegaly is the consequence and not the cause of the hyperbilirubinemia, as the inconstant results produced by splenectomy seem to prove

Widal and his associates consider that the primary cause of hemolytic jaundice is the alteration of the red blood cells due to hemolysins fixed on their surface, which renders them more susceptible to destruction These hemolysins may be either of exogenous or endogenous origin The presence of hemolysins in the pathologic spleen has not as yet been demonstrated In four cases of splenectomy for hemolytic jaundice, those of Vaquez and Giroux (271), Antonelli (8) and two of Kahn (120), hemolysins have not been demonstrated The following questions present themselves for analysis

Is hemolytic jaundice of strictly hemolytic nature? Is there only overproduction of bilirubin without any hepatic lesion? Widal and his associates deny any participation of the liver cell since the carbohydrate tolerance test, and the Widal test have been negative in cases studied by them But how is it possible to draw conclusions about the functional efficiency of the bilirubin excretory power of the liver cell from the results of tests which measure quite different functions? Can there not be isolated dysfunction? The existence of such states in liver pathology is beyond doubt

The production of a liver lesion by the action of uncomplicated anoxemia, a lesion which produces a delayed excretion of bilirubin injected intravenously and the presence of this same disturbance in pernicious anemia, strongly suggests similar functional impairment of the liver cell in hemolytic jaundice, especially in its late stages, when anemia is always evident

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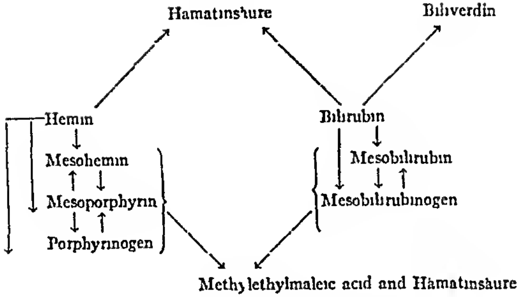
Briefly these processes can be tabulated, as suggested by Fischer, as follows



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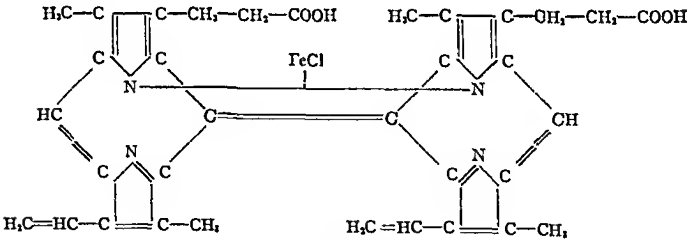
As these reactions constitute a series of hydrolytic processes, Kuster simplifies them in the following schematic formula

$$\text{Hematin} + 2H_2O = \text{Bilirubin} + FeO$$

The relation between the pigments of the blood and bile is further indicated by the accompanying structural formulae for hemin and bilirubin, according to the views of Fischer, which have been recently confirmed by his brilliant studies on the synthesis of hemin and porfirins (75)



Hemin

BILIRUBINEMIA

E. S. GUZMAN BARRON

From the Chemical Division of the Medical Clinic of the Johns Hopkins University, Baltimore

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INTRODUCTION

The recent advances in the knowledge of the group of diseases in which there is impairment of bilirubin excretion, have been made through the cooperation of chemists, physiologists, pathologists and clinicians, and these painstaking investigations, particularly during the last thirty years, have enabled us to build the foundations of our present conception of the problem of jaundice. The older views on jaundice, which were based only on anatomical grounds, have been recently so thoroughly revised, that the writer feels it will be best to pass in review some of the outstanding physiological and chemical researches, before dealing with the methods of determination of bilirubinemia and its clinical applications.

CHEMICAL ORIGIN OF BILIRUBIN

Virchow (272) in 1847 was the first to suggest the chemical similarity of bilirubin and hemoglobin, for he discovered in old foci of hemorrhage

a pigment closely related to bilirubin, to which he cautiously gave the name of "hematoidin" Three years later Herrmann (103) demonstrated that intravascular hemolysis, by means of the injection of distilled water, would lead to the subsequent excretion of bilirubin in the urine Tarchanoff (261) extended these observations by injecting hemoglobin itself intravenously, and collecting the excreted bile through a biliary fistula An increased output of bile resulted The chemical identity of the pigment formed when hemoglobin is liberated intravascularly (bilirubin) and the pigment formed when hemoglobin is liberated extravascularly (hematoidin) now seems well established as a result of the experiments of Rich and Bumstead (224) on a sample of hematoidin found in an old hemorrhagic cyst

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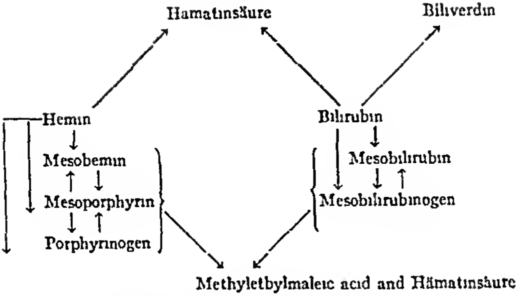

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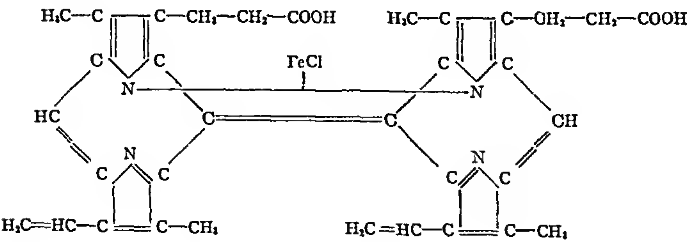

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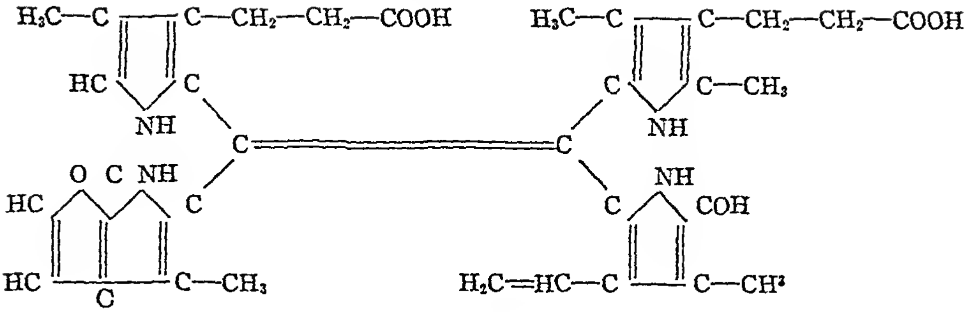
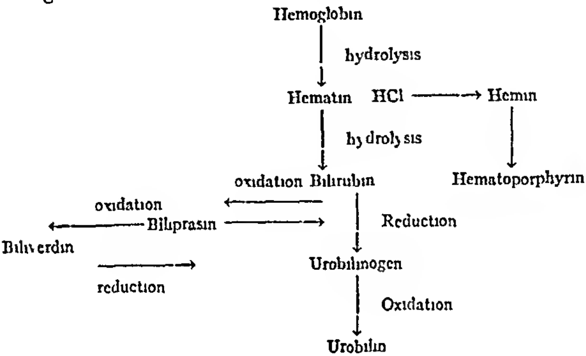


Bilirubin

Blood hemoglobin seems therefore to be the main source of supply for the formation of bilirubin It is possible that other compounds, containing the pyrrol nucleus in their structure, could be changed into bilirubin Whipple and Hooper (284, 285), and more recently Whipple and Robscheit (286), state that myohemoglobin is another source of bilirubin If Kennedy and Whipple's statement (125), that blood hemoglobin and muscle hemoglobin are identical, since both give similar spectrophotometric curves, is confirmed, it is obvious that muscle hemoglobin may also take part in bilirubin formation Whipple and Hooper's assertion that the output of bilirubin in dogs increases after a diet rich in carbohydrates has been denied by Inlow (115), and Rous (237), who reported that in their experiments with bile fistula dogs, a diet rich in carbohydrates had no effect upon the amount of bile pigment formed There is a close relationship between the chlorophyll molecule and hematin (Willstater and Stoll (282)), and Noack (204), in beautiful experiments, has recently shown that bilipurpurin, a pigment present in small amount in the bile of herviborous animals, has essentially the same chemical constitution as photopheophitin, a pigment derived from chlorophyll This would favor the possibility of an exogenous origin of bilirubin The statement of Bollmann, Sheard and Mann (24) that they were unable to detect any alteration in bilirubin formation after the intravenous injection of chlorophyll in dogs, does not exclude the possibility of bilirubin formation from chlorophyll, since, in the case of intravenous injections, the excretory power of the liver rapidly frees the blood of the injected pigment

The following table taken from Rolleston and McNee (231) gives a short summary of the relationship of bilirubin, and its derivatives, to hemoglobin



PHYSIOLOGICAL ORIGIN OF BILIRUBIN

Since Rich's splendid review (225) on the formation of bile pigment, few facts have been brought to light bearing upon the exact origin of bilirubin

Virchow's original view (272) which came as a consequence of his observation on hematoidin, was that bilirubin could be formed outside the liver, as the pigment he found in old blood extravasations, had a close resemblance to bilirubin The celebrated experiments of Minkowski and Naunyn (186) on the absence of jaundice in hepatectomized geese, in which intravascular hemolysis had been produced by arseniureted hydrogen, were so widely accepted for a time, that the liver came to be considered as the only site of bile formation The work of Minkowski and Naunyn remained unchallenged until McNee (183, 184), repeating and confirming their experiments, explained them in a very different way, stating that the prevention of icterus was probably due to the removal by the hepatectomy of the phagocytic Kupffer cells, rather than to the loss of the polygonal cells of the liver The remarkable series of studies of Mann and his coworkers (160–164) on the physiology of the liver, in which they demonstrated the ap-

pearance of bilirubin in the blood of hepatectomized dogs, an observation amply confirmed by Makino (159), Rich (226) and others, proved conclusively that in dogs, at least, bile pigment continues to be formed, and to accumulate in the blood stream, after the liver, or, indeed, after all the abdominal viscera have been removed (Rich)

As a consequence of these fundamental observations attention was directed towards the extrahepatic formation of bilirubin Lepehne (148) attempted to prove that the pigment is formed by the reticulo-endothelial cells, stating that after overloading these cells with collargol the process of bile pigment formation was less active Rich (227), by the methods of tissue culture, was able to prove that only mesodermal, and not ectodermal or endodermal cells can transform hemoglobin into bile pigment and that this process occurs within the cells Numerous attempts by Rich and Bumstead (224) to prove the existence of some extracellular enzyme which can influence the transformation of hemoglobin into bilirubin, gave uniformly negative results It is therefore probable than when bilirubin is formed from hemoglobin within the phagocytic cells, as in Rich's experiments, the process is carried on by a cellular hydrolytic ferment

Confirming Van den Bergh's early investigations, Ernst and Szappanyos (61) and Komori and Ywao (134) observed the formation of bilirubin following the injection of hemoglobin into the perfused, asphyxiated spleen, and Mann, Sheard, Bollman and Baldes (161) reported that the injection of hemoglobin into the blood, entering the spleen and bone marrow, produces an increase in the amount of bilirubin formed at these sites Mann, Sheard and Bollman (162) measured the relative amounts of bilirubin formed in the liver, spleen and bone marrow, concluding that in dogs the spleen produces more bilirubin than the liver, that even in the absence of the liver and spleen, bilirubin continues to be formed at its normal rate, which would lead to the conclusion that the bone marrow can take over the function of bilirubin formation in the absence of the other sources of formation. Whether bilirubin formation can be inhibited by suppression of the bone marrow has not yet been determined

All these concordant experiments seem to prove conclusively that there is an extrahepatic origin for bile pigment It is true, that recently Melchior, Rosenthal and Licht (182, 234, 235), working in

Naunyn's laboratory, in a series of papers revert to Minkowski and Naunyn's original hypothesis, and consider the liver as the main organ of bilirubin formation Their conclusion was drawn from the fact that the jaundice, which invariably follows the injection of toluilendiamine in control dogs, does not appear in hepatectomized animals When the liver is removed, after jaundice has appeared as a consequence of toluilendiamine injection, the bilirubin in the blood not only ceases to increase but actually decreases These facts, however, are not actually incompatible with the extrahepatic origin of bilirubin, for Joannovick and Pick (117) and others, have shown that toluilendiamine produces necrosis of the liver cells This form of jaundice is therefore dependent upon the presence of the liver, as we shall see below, but not in the sense that the liver cell produces the pigment

In summary it can be stated that

1 There is no evidence that the polygonal liver cells are concerned with the formation of bilirubin All the experiments performed in recent years are decidedly against such evidence

2 There is no evidence that there exists an extracellular enzyme capable of transforming hemoglobin into bilirubin It is probable, though not conclusively proved, that this process is carried on by a cellular hydrolytic enzyme

3 The cells of the reticulo-endothelial system are in all probability actively concerned in the formation of bilirubin

METHODS OF BLOOD BILIRUBIN ESTIMATION

Since the classical researches of Gilbert and his associates, many methods have been suggested for the determination of bilirubin in the blood They can be divided into the following groups

1 Estimation based on the oxidation of bilirubin
2 Direct comparative estimation of the colour of blood serum
3 Methods based on the use of Ehrlich's diazo-reagent
4 Spectrophotometric methods

1 Methods based on the oxidation of bilirubin

Gilbert, Herscher, and Posternack (84), in 1903, were the first to elaborate a method for the estimation of serum bilirubin Oxidizing

the bilirubin into biliverdin by means of Gmelin reagent, and comparing the intensity of the colour reaction, they were the first to demonstrate that bilirubin was normally present in the blood serum Later, Hertzfeld (105) applied the same principle using Hammarsten's reagent (1 volume of 25 per cent HNO_3 + 19 volumes 25 per cent HCl, after 24 hours add to 1 volume of this solution, 4 volumes of alcohol), but his figures are subject to the same sources of error as Gilbert's estimations More reliable and simple is the method proposed by Fouchet (78), who oxidizes the bilirubin by a solution containing trichloroacetic acid and $FeCl_3$ (trichloroacetic acid, 5 grams, $FeCl_3$ 10 per cent, 2 cc , distilled water, 20 cc) Equal parts of serum and reagent are taken, the reagent being added to the serum drop by drop, after stirring with a glass rod, the green colour obtained is compared with a previously made colour chart The sensitivity of the method according to Fouchet is 1 × 60,000 The methods of Posselt (214) and Biffi (21) are based on the same principle of oxidation of bilirubin by acids

The figures obtained using these methods are not reliable, not only because the comparisons with the artificial standards are too roughly approximate, but chiefly because the methods are not sensitive enough

2 Direct comparative estimation of the colour of blood serum

Assuming that the yellow colour of the blood serum is principally due to bilirubin, methods have been evolved to determine the amount of bilirubin by comparing the colour of the serum with artificial standards of approximately the same shade of yellow colour

Meulengracht (179), who was the originator of these methods, employs a standard solution containing 1 10,000 of potassium dichromate plus 2 drops of H_2SO_4 per every 500 cc of solution He dilutes the serum with physiological salt solution until the colours can be compared He obtains thereby a comparative figure which he calls the colorimetric index, giving 1 to 10 units as a normal index [1] The same technique has been recommended under the name of "icterus index" by Maue (170)

[1] For example, if 1 cc of serum is diluted to 25 cc and the standard read 17 5 when the unknown is set at 20, the icterus index is 21 9

and Bernheim (19) They use the colorimeter for the comparison, their calculation being

$$\frac{\text{Reading of standard}}{\text{Reading of unknown}} \times \text{dilution} = \text{icterus index}$$

They state that the normal icterus index lies between 4 and 6 Walter (273) uses, as a standard, a mixture of potassium bichromate (1 10,000) 100 cc and "orange poirier" (1 10,000) 2 cc He employs plasma instead of serum

Ernst and Forster (62) precipitate the serum with two volumes of acetone, and after filtration, they make the comparison in a colorimeter with the dichromate standard so diluted as to make a proper colorimetric reading

As the chemistry, the amount and the daily variation of the lypochromes (lutein, carotin, etc) of the blood is unknown the writer is of the opinion that these methods in which bilirubin as well as all other yellow substances also present in the blood serum are estimated, ought to be discarded It is well known that the yellow colour of the serum increases with a diet rich in vegetables Stoner's (257) studies on carotinemia, so common in children, Fiessinger, Walter, and Thierry's (66) studies on the effect of carotinemia on xanthochromia of plasma, and Rabinowitch's (218) and Hess and Myers' (108) reports of high carotinemia in diabetic patients as well as Hernando's (102) contribution on pseudo-jaundice from carotin pigment should warn the clinician against the employment of the colour of blood serum as an index to bilirubinemia

3 *Methods based on Ehrlich's reaction*

Ehrlich, as early as 1883 (55), discovered that a mixture of sulfanilic acid, HCl and sodium nitrite (diazonium salt) gave a red violet colour when added to solutions containing bilirubin The chemistry of the reaction remained unknown until 1900 when Proscher (217) clearly established the fact that bilirubin combines with the diazobenzolsulphochloride (Ehrlich's diazo reagent) to form acetophenolazorubin, whose formula and spectral bands in different solutions he determined More recently, Kerppola and Leikola (124) describe 13 different stages of oxidation, when Na nitrite and HCl were added to

bilirubin dissolved in chloroform. They show that the colour of Ehrlich's diazo-reaction is due partly to oxidation and partly to the action of acid. Notwithstanding the importance of Ehrlich's discovery and Proscher's demonstration of the specificity of such a reaction for the estimation of bilirubin, it was only many years later, in 1913, that Van den Bergh and Snapper (270) employed Ehrlich's diazo-reaction for the estimation of blood bilirubin. Van den Bergh and his co-workers, by the adaptation of Ehrlich's diazo test to the determination of bilirubinemia, opened up an entirely new approach to the experimental investigation of bile pigment metabolism. This test is not only of great assistance because of its delicacy and accuracy in quantitative work, but also because qualitative differences in the behaviour of the reaction serve to differentiate various forms of jaundice.

Qualitative Van den Bergh reaction. Van den Bergh and Müller (266) discovered that in some cases of jaundice, especially those of the obstructive type, the red violet colour develops immediately after the addition of Ehrlich's diazo-reagent to the blood serum; while in other cases, namely, those of hemolytic nature, the addition of alcohol is necessary to produce the formation of diazo-bilirubin. This led to their well known separation of the reaction into the "direct" type, characteristic of obstructive or "mechanical" jaundice, and the "indirect" type, characteristic of non-obstructive or "dynamic" jaundice. Feigl and Quarner (64) have further pointed out that besides these two types of reaction, there is a "biphasic reaction" which will be described later.

Everyone who has had experience with the Van den Bergh reaction has been able to confirm Feigl and Quarner's type of biphasic reaction, a distinction important to retain, especially when following the progress of jaundiced patients.

Technique of the Van den Bergh reaction. Collection of blood: Blood serum or plasma is equally suitable. As it is more difficult to avoid hemolysis when blood is allowed to clot, plasma is more convenient, using 0.2 cc. of a 10 per cent solution of potassium oxalate (evaporated to dryness) for 10 cc. of blood as anticoagulant. There are no differences in the readings whether plasma or serum is used. The blood has to be fresh as the bilirubin oxidizes on standing and the quality of the reaction may change. Test tubes and pipettes used have to be *perfectly* clean.

Reagents —

Solution A

Sulphanilic acid	0 1 gram
Concentrated HCl	1 5 cc
Distilled water	100 cc

Solution B

Sodium nitrite	0 5 gram
Distilled water	100 grams

Both solutions ought to be renewed every 15 days

To perform the reaction one mixes 5 cc of solution A and 0 1 5 cc of solution B (This mixture has to be freshly made) Tev?

Qualitative reaction One cubic centimeter of oxalated plasma (or serum) is placed in a small test tube and 0 5 cc of the diazo-reagent added The appearance and development of the colour reaction is watched and timed

Direct reaction The colour appears immediately after the addition of the reagent and acquires its maximum intensity 30 seconds later

Biphasic reaction The colour reaction appears at once as in the first type or within 30 seconds but its *maximum intensity* is reached after a variable time If the colour reaches its maximum intensity quite rapidly the reaction is called "prompt biphasic," while it is called "delayed biphasic" when the colour deepens quite slowly

Indirect reaction The colour reaction appears one or more minutes after the addition of the reagent The maximum intensity is reached at variable times and the addition of alcohol is essential to obtain the maximum colour

Quantitative determination Standard solution The standard employed is a solution of cobaltous sulphate If dryed anhydrous cobaltous sulphate is used, take 21 610 grams in 1000 cc of distilled water If crystallized cobaltous sulphate is used ($CoSO_4 7H_2O$), take 39 150 grams in 1000 cc of distilled water This standard is taken by Van den Bergh as equal to 1 unit This corresponds to $\frac{1}{200\,000}$ of bilirubin, i e , 0 5 mgm per cent

A Serum or plasma giving indirect reaction Take 1 cc of serum and 2 cc of alcohol (96 per cent) Shake and centrifuge One cubic centimeter of the supernatant fluid is taken into a test tube and 0 25 cc of the reagent and 0 5 cc of alcohol added Compare the colour with the standard in any microcolorimeter

Calculation In the first dilution we would have a 1 3 dilution but as a result of the contraction due to alcohol this dilution is only $\frac{20}{7}$ In the second dilution we have $\frac{7}{4}$. The final dilution will be $\frac{20}{7} \times \frac{7}{4} = \frac{1}{5}$

Therefore.

$$\frac{\text{Reading of standard}}{\text{Reading of unknown}} \times 5 = \text{units} \times \tfrac{1}{2} = \text{mgm bilirubin per cent}$$

B Serum giving biphasic reaction or low bilirubin content with direct reaction Thannhauser and Andersen's modification is recommended: To 1 cc of plasma or serum add 2 5 cc alcohol (96 per cent) and 1 cc of a saturated solution of $(NH_4)_2SO_4$ Shake and centrifuge

Calculation

$$\frac{\text{Reading of standard}}{\text{Reading of unknown}} \times 4 = \text{units} \times \tfrac{1}{2} = \text{mgm bilirubin per cent}$$

If the colour of the unknown is too strong, dilute with 2 parts of alcohol and 1 part of water

C Serum having high bilirubin content (direct reaction) Mix 0 5 cc. plasma or serum and 0 5 cc reagent Add water (varying measured quantities to get a reasonable dilution) and then add alcohol so that the fluid is increased thrice its bulk Centrifuge and read in the colorimeter

Calculation:

$$\frac{\text{Reading of standard}}{\text{Reading of unknown}} \times \text{dilution} = \text{units} \times \tfrac{1}{2} = \text{mgm per cent}$$

Modifications of Van den Bergh's technique Two objections have been raised against the Van den Bergh method

1 That it is extremely difficult to obtain a colour reaction which would be entirely comparable to the standard

2 That during the precipitation of the plasma proteins by alcohol, some of the bilirubin is adsorbed by the protein In regard to the first objection, the writer thinks that the utmost care must be taken not to alter the final pH of the solution As the diazobilirubin responsible for the colour reaction behaves like an indicator dye, its colour changes from the blue at the acid side to the yellow on the

alkaline side When perfectly clean tubes and pipettes are used and the proper amounts of reagents are added, the pH of the final solutions is always around the optimum for the production of the red violet colour and no difficulties are encountered With increasing acidity the colour changes to violet first, then to blue, greenish blue and green (oxidation to biliverdin) When the reaction is toward the alkaline side, the colour becomes red, red brown, and yellow Thannhauser

TABLE 1

Comparative blood bilirubin estimations by the Van den Bergh technique and the Thannhausen and Andersen's modification

TYPE OF VAN DEN BERGH REACTION	SERUM BILIRUBIN		PER CENT OF BILIRUBIN ADSORBED BY THE ALCOHOLIC PROTEIN PRECIPITATE
	Van den Bergh technique	Thannhauser and Andersen's technique	
	mg per cent	*mg per cent*	
I Indirect			
Hemolytic jaundice	8 70	9 00	3 0
Pernicious anemia	2 85	2 95	3 4
Malaria	2 00	2 00	0 0
II Biphasic			
Lobar pneumonia	2 04	3 80	20 0
Catharral jaundice	4 00	6 00	33 0
Arsphenamin jaundice	3 00	4 80	37 0
III Direct			
Gall stones	8 00	14 00	42 8
Carcinoma of pancreasinoma	7 00	13 50	48 0
Cholecystitis	3 62	6 51	29 0

and Andersen (264), Greppy and de Micheli (91) advise the acidification of the solution in order to have a blue colour

The second objection is more serious Van den Bergh himself pointed out that when the proteins of serum giving direct and indirect reaction are precipitated with alcohol, the bilirubin, giving the direct reaction, is more easily adsorbed by the protein precipitate than the bilirubin giving the indirect reaction The figures in table 1 taken from numerous concordant determinations, give a clear comprehension of this different behaviour The plasma bilirubin was estimated by the original Van den Bergh technique (alcohol precipitation) and Thann-

hauser and Andersen's modification (264) in which the protein adsorption is loosened by salting out the proteins by a saturated solution of ammonium sulphate

Thannhauser and Andersen's modification in which all the bilirubin goes into solution is therefore to be recommended especially in cases where there is a biphasic reaction or a high indirect reaction

Enriquez and Sivo (57) raise another objection to the Van den Bergh reaction, namely, that in cases of hypobilirubinemia the high dilution required in Van den Bergh's technique makes a colorimetric reading almost impossible, and they propose the following modification To 0 5 cc of serum they add 0 5 cc of a solution of sodium benzoate caffeine (20 per cent) and 0 2 cc of the diazo-reagent The colour is compared to a standard made with a bilirubin solution (0 01 per cent in N/100 NaOH) They avoid protein precipitate, but their final colloid suspension cannot be compared colorimetrically

4 *Spectrophotometric methods*

Huffner was the first to determine bilirubin in this way but Sheard, Baldes, Mann, and Bollmann used the method more extensively (251) There is no doubt that it is by far the most accurate and sensitive way of measuring bilirubinemia, but the cost of the instrument and the careful technique which it requires, makes it unsuitable for clinical work Mann and his co-workers use the Keuffel and Esser colour analyzer which has the advantage over ordinary spectrophotometers of being easier to manipulate As the percentage of light transmission changes with time, they recommend that the alcoholic solutions of serum bilirubin be prepared, and that the readings of wavelength and percentage transmission be made as rapidly as possible in the region of 430 to 500 Comparing this method with the Van den Bergh method, they find that it is possible to determine the character and the shape of the spectrophotometric curve of bilirubin for a dilution as low as one fiftieth of the smallest amount measurable by the Van den Bergh technique

THE NATURE OF THE VAN DEN BERGH REACTION

The nature of the Van den Bergh reaction has aroused considerable attention, since it is generally agreed that the different types of reaction correspond to perfectly distinct groups of jaundice

Van den Bergh (267) proposed two alternative theories (1) That there may be differences in the chemical composition of the bilirubin normally circulating in the blood stream, and in that of the bilirubin which has passed through the liver cell (2) That in the indirect type of reaction the bilirubin is bound up in some manner with the blood proteins or lipoids so as to prevent it from coupling with the diazo-reagent The advocates of the first theory have accumulated evidence of certain physical and chemical differences between the "direct" and "indirect" types of the Van den Bergh reaction these differences are as follows

First That, as pointed out by Van den Bergh (269) and Andrews (7), the bilirubin of serum giving the direct reaction oxidizes more easily than the bilirubin from the serum giving the indirect reaction

Second That when the proteins of both kinds of sera are precipitated with alcohol, the bilirubin giving the direct reaction is more easily adsorbed by the protein precipitate than the bilirubin giving the indirect reaction (Van den Bergh)

Third That when the two types of sera are shaken with chloroform, the "indirect" bilirubin passes into solution into the chloroform while the "direct" bilirubin does not (Grunnenberg (93))

Fourth That the bilirubin from obstructive jaundice is dialyzable through a collodion membrane, while the bilirubin from hemolytic jaundice is not (Hoover and Blankenhorn (111), Brule, Garban and Weissman (29), Leschke (151))

Andrews, reviewing these differences, concludes that the bilirubin giving the indirect reaction is in fine suspension instead of in true solution, or that possibly it is a polymer of the "direct" type While the first three differences may be verified, the writer has been unable to confirm any difference in the dializability of bilirubin whether from obstructive jaundice or from hemolytic jaundice

Collinson and Fowweather (38), accepting the formula for the composition of bilirubin suggested by Fischer (74), who regards it as an acid with two carboxil groups, capable of forming salts which will differ in certain properties from the free acids, says "while the bilirubin giving the prompt direct reaction is an alkali salt which we believe is probably the ammonium salt, the form which is responsible for the indirect reaction is the free acid present in the blood in a colloidal state" The

writer has been unable to confirm Collinson and Fowweather's experiments The serum giving the direct reaction could not be converted into one giving the indirect reaction by the addition of hydrochloric acid, and only in rare cases did the addition of ammonia to sera giving the indirect reaction hasten the reaction with the diazo-reagent Davies and Dodds (49), who made an interesting study of the limits of hydrogen ion concentration between which the reaction of the diazo-reagent and bilirubin takes place, state that the indirect reaction is produced by oxidized bilirubin, i e , biliverdin, but biliverdin does not give the Van den Bergh reaction Roberts (230) believed that the "indirect" bilirubin is in free colloidal condition, and the "direct" bilirubin is in combination with some substance "the nature of which is as yet undetermined " Newmann (203) concludes from his experiments that the difference between these two types of the Van den Bergh reaction is due to an underlying chemical difference between the bilirubins

Among the advocates of the second theory, Adler and Strauss (5), in a series of papers speak of a physico-chemical change in the state of serum proteins, namely a change in the $\frac{\text{globulin}}{\text{albumin}}$ ratio, which, according to them, would be considerably lowered in cases of obstructive jaundice, while it would be normal in hemolytic jaundice Some of the authors' experiments are interesting and have been confirmed by the writer, such as the influence of temperature, the addition of alcohol, of salts of caffein, in accelerating the reaction. The assumption that the $\frac{\text{globulin}}{\text{albumin}}$ ratio plays an important rôle in the behaviour of the Van den Bergh reaction is unwarranted, as the Van den Bergh reaction changes from the indirect type into the direct in one, four or five hours after biliary obstruction (Barron and Bumstead) without any change in the G A ratio Feigl and Querner (64) suggest a possible lipoid linkage as an explanation for the indirect type of bilirubin, which Andrews was unable to confirm Levi-Crailsheim (154) supports the theory of protein-linkage stating that serum giving the indirect Van den Bergh reaction will give a direct reaction after digestion with pepsin, pancreatin or even liver extracts The writer has been unable to confirm these findings Neither commercial pepsin nor pancreatic

extract proved to be active, had no effect in accelerating the rate of the reaction. Thannhauser and Andersen (264) state that the addition of bile salts, or mixtures of cholesterol and bile salts, can change a serum giving the indirect reaction into one giving the direct reaction. Adler and Strauss (5), as well as several other investigators, were unable to confirm this statement. Bollmann, Sheard and Mann (24), made an important contribution to the theory of the chemical identity of these two types of reaction by demonstrating that alcohol-acetone solutions, and even aqueous solutions of icteric serum from patients having obstructive and hemolytic jaundice, gave the same curve of light transmission when measured spectrophotometrically. Nevertheless, in their conclusions concerning the difference of these two types of reactions, they state that "it might appear that the direct reaction of obstructive jaundice is due to the retention in the blood of a substance which destroys this linkage of bilirubin with serum."

The writer, while investigating the problem (14), has made use of solutions of bilirubin and normal serum, having thus two controlled factors: bilirubin and serum, each of the same chemical constitution. When sodium bilirubinate, buffered to pH 8.43[2] and giving a direct Van den Bergh reaction is added to normal human blood serum in increasing amounts up to 12 mgm. per cent, a typical indirect reaction is obtained. When the concentration of bilirubin is increased to 16 mgm. per cent, the reaction becomes of the biphasic type, i.e., the colour appears twenty seconds after the addition of the diazonium salt, reaching its maximum intensity two minutes later. When the bilirubin concentration is higher than 16 mgm. per cent, a direct reaction is obtained. The following conclusions can be formulated from these experiments. Some constituent of the serum has a tendency to adsorb bilirubin, and this adsorption of bilirubin prevents the immediate coupling with the diazonium salt. Much has been written in regard to the forces which are operating on the surfaces to cause these adsorption effects. One group of workers has taken the viewpoint that the reactions are purely physical, while others have insisted that the forces are those of chemical union. It is no longer expedient to lay great stress upon this difference, since molecular attraction of every degree

[2] Bilirubin is dissolved in N/20 NaOH and 4 M phosphate mixtures of pH 7.00 added. The bilirubin remains in solution for some minutes only, after which it precipitates.

Monge (194) has found an increase in the bilirubin content of the blood some days after residence at high altitudes The over-activity of the blood forming and blood destroying tissues observed under those conditions, together with the effect of anoxemia to be discussed below might possibly explain this observation

The hyperbilirubinemia of infants is well known Thus from fifty newborn infants examined, Meyer and Adler (177) found only fifteen without signs of jaundice. The bilirubin content of those infants without jaundice fluctuated from 0 6 to 0 9 mgm per cent in the blood

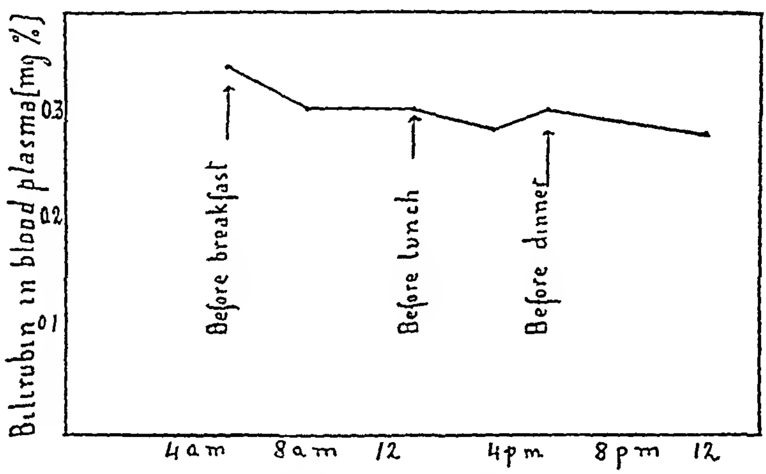


Fig 1 Daily Variations of the Blood Bilirubin

taken from the arm, while the blood from the umbilical vein gave higher figures (from 0 9 to 2 1 mgm per cent)

Sex seems to have no influence, although Schiff (252) states that bilirubinemia is higher in males than in females The writer has been unable to confirm this observation

PATHOLOGIC ALTERATIONS OF BILIRUBINEMIA

The maintenance of the concentration of the blood bilirubin within normal limits is a result of the interplay of different factors which enter into the production and excretion of the pigment The number of erythrocytes in the blood and the rate of their destruction; the function of the reticulo endothelial system and the polygonal liver

the blood serum, presence of bilirubin in the urine, absence or scarcity of bile pigments in the stools (2) *Non-obstructive jaundice* where the primary and initial cause of the syndrome depends upon a deficiency of the bilirubin excretory function of the polygonal liver cells, an insufficiency produced by the action of bacterial or non-bacterial toxins or by prolonged anoxemia Very rarely an enormous overproduction of bilirubin can also produce this type of jaundice

Seldom is this type of jaundice, which is merely a functional cellular insufficiency maintained in the initial phase During this period it will be characterized by hyperbilirubinemia, an indirect Van den Bergh reaction, absence of bilirubin in the urine, increased bilirubin in the stools and the presence of urobilin in the urine Generally the pathologic process advances further and as a consequence, there is actual destruction of the hepatic polygonal cell, eventually leading to discontinuity and derangement of the bile canaliculi During this second stage, the Van den Bergh reaction will be direct and bilirubin will be found in the urine, as will be explained later.

A Obstructive jaundice

The mechanism of complete obstructive jaundice in its early stages has recently been studied by Bumstead and the writer (12) After ligating the ductus choledochus, and cystic duct of dogs, we measured the blood bilirubin at different intervals and observed the Van den Bergh reaction The results were as follows first, there was an increase of the indirect Van den Bergh reaction, which appeared usually between the beginning and end of the second hour after obstruction Following this period the biphasic reaction appeared and usually lasted one to two hours Finally the direct reaction appeared 4 to 5 hours after obstruction, and remained as long as the obstruction persisted (figs 2 and 3) When obstruction was released, the sequence of the Van den Bergh reaction was reversed, i e , the direct reaction was replaced by the biphasic, then by the indirect and finally the reaction became negative (the dog has normally a negative Van den Bergh reaction) It was suggested that the first increase of the indirect type of reaction was due to a temporary reflex inhibition of the liver cell function due to ligation of the ducts This is comparable to the reflex anuria which may occur when the ureter is ligated It was also found

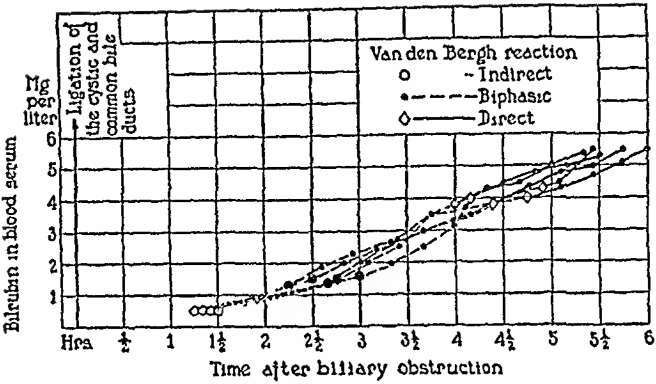


FIG 2 EXPERIMENTAL OBSTRUCTIVE JAUNDICE IN NEPHRECTOMISED DOGS CURVE OF BLOOD BILIRUBIN AND VAN DEN BERGH REACTION IN EARLY OBSTRUCTIVE JAUNDICE

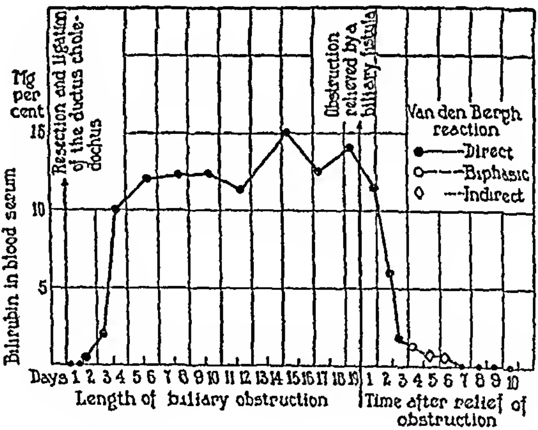


FIG 3 EXPERIMENTAL OBSTRUCTIVE JAUNDICE IN DOGS CURVE OF BLOOD BILIRUBIN DURING THE WHOLE PERIOD OF OBSTRUCTION TILL 7 DAYS AFTER RELIEF OF OBSTRUCTION BY A BILIARY FISTULA

that the direct reaction appears before any rupture of the bile capillaries is visible As the bile capillaries are dilated they extend between the liver cells as small distended pouches, the blind ends of these lying in contact with the capillary spaces Then diffusion of bile from these thin walled pouches into the perivascular spaces takes place, diffusion being favored by the mounting pressure within the bile ducts (as found by Bollmann, Sheard and Mann (24)) The latter was given as an explanation of the appearance of the direct Van den Bergh reaction These experimental studies have been confirmed by Mayo and Green (171), and they also have been frequently confirmed in this clinic, by the observation of numerous cases of obstructive jaundice, and especially those produced by gall stones where, when the jaundice begins to diminish the direct Van den Bergh reaction is changed into biphasic and then into indirect

The mechanism of complete obstructive jaundice of long standing is fairly well understood As shown by Eppinger (58) for the first time, and confirmed by Abramow and Samoilowicz (4) the bile canaliculi, in these cases, are distended and tortuous, and as their walls are frequently ruptured, the bile empties into the peri-vascular lymph spaces Associated with this, some necrosis of the liver cells accompanies obstructive jaundice (Ogata (207))

Obstructive jaundice can, therefore, be satisfactorily explained As the first period of hyperbilirubinemia associated with the indirect Van den Bergh reaction lasts only for a few hours, it can, for practical purposes, be discarded Obstructive jaundice may be characterized in the laboratory by hyperbilirubinemia with direct Van den Bergh reaction, the presence of bilirubin in the urine as soon as the renal threshold has been exceeded (about 2 mgm per cent of blood bilirubin), and the absence or scarcity of bile pigments in the stools Jaundice here appears more promptly than in the second group, probably because of the physico-chemical condition of the bilirubin in the blood As it remains free from adsorption by the serum proteins, it is more easily diffusible and thus stains the tissues in general, and the skin and mucosas in particular, more quickly than in the second group The degree of bilirubinemia will depend on the length of time and degree of obstruction, being more pronounced in cases of complete obstruction, and will follow the same course as that observed in experimental

obstructive jaundice (fig 3) Obstructive jaundice may be caused by the following pathologic conditions (1) An obstacle inside the lumen of the bile ducts, (2) alteration of the walls of the larger ducts, (3) a compression of the duct

Among the first group, the most common cause of jaundice is *cholelithiasis* Usually it is accompanied by all the symptoms of obstructive jaundice Sometimes, however, it gives only slight transient jaundice (Meulengracht (181)), in which case the direct Van den Bergh reaction can be of diagnostic importance According to Kehr (123) about 30 per cent of all gallstone cases and 75 per cent of common duct stone cases have a history of jaundice Takata (260) reports 15 cases of biliary colic examined during or shortly after the attack in every one of which an increase in the amount of bilirubin was found without the presence of visible jaundice

Parasites may produce obstructive jaundice Mertens (174) reports 48 cases in which *Ascaris lumbricoides*, entering the common bile duct from the duodenum, produced jaundice Recently, Labbé and Denoyelle (141) Fiessinger (68) and Panayotatou (209) have reported similar cases *Hydatids* (*Taenia echinococcus*) are a frequent cause of obstructive jaundice in cattle raising regions Castex, Romano and Beretervide (34) have related cases of hydatid cyst resembling the classic forms of obstructive jaundice

Jaundice due to hydatid cysts can be produced in the following ways (1) by rupture of the cysts into the lumina of bile ducts, (2) by mechanical compression of the bile ducts by a cyst developing in the interior portion of the liver (3) by complicated infections of the cyst or its surroundings (Trias Pujol (265)) *Faciola hepatica* (*Distomum hepaticum*), *Opisthorchis Sinensis* and *Opistohorchis noverca* have been found in the bile ducts (Rolleston and McNee (231))

The most common cause among the second group is *cholangitis* In its infective and suppurative form, it is usually associated with gallstones Kretz (136) describes under the name of *Icterus duodenalis* a type of jaundice produced by inflammatory swelling of the duodenal mucosa and subsequent inflammation of the end portion of the ductus choledochus Cruvelhier (43) states that scars produced by the cicatrization of duodenal ulcer can give place to a stenosis of the ductus choledochus Moyniham (197) reports 11 cases in which there was

jaundice consequent to cicatrical contraction of the duodenal ulcer involving the papilla (see also Bickel (20)) Beingolea (18) reports a case of jaundice produced by duodenal diverticulum Primary tumours of the bile ducts, though rare, (Miller (189)) are among this group *Atresia* and *congenital stenosis of the bile ducts*, sometimes seen in infants, (Frensdorf (81) and Hallez, (96)) are also causes of obstructive jaundice

Among the third group there are in the first place, tumours compressing the bile ducts *Primary tumous of the liver* give rise to obstructive jaundice only when by their growth they compress large bile ducts (Counseller and McIndoe (41), Smith (254)) This is in accordance with the observation of McMaster and Rous (185), on the amount of biliary obstruction required to produce jaundice The bile ducts from three fourths of the liver substance in dogs and monkeys could be obstructed without any clinical evidence developing of pigment or cholate accumulation in the organism

Malignant tumours of the duodenum, especially of the papilla of Vater (Letulle (152)) are accompanied by jaundice In some cases of *tumours* of the *papilla of Vater*, Carnot (37) has observed intermittent jaundice before the development of a permanent jaundice *Malignant tumours involving the head of the pancreas* are frequent causes of jaundice (Fowler (78)) Millarié (190) finds that jaundice occurred in 82 cases out of 113 cases of tumours of the pancreas Whether *chronic pancreatitis* will or will not compress the common bile duct depends on the anatomical relation of the ductus choledochus to the head of the pancreas In 38 per cent of the cases the duct passes behind the head of the pancreas, and in these cases chronic pancreatitis need not compress the common bile duct In 62 per cent of the cases the common bile duct is imbedded in the head of the pancreas (Helley (101)) and in these cases jaundice usually occurs *Gummatous infiltrations* in and around the head of the pancreas cause rare cases of jaundice, *Pancreatic cysts* seldom press on the liver ducts and produce jaundice (McPhedran (186)). *Hemorrhagic pancreatitis* may be associated with jaundice *Large pancreatic calculi* in the ampulla of Vater or in the termination of Wirsung's duct, compressing the terminal part of the common bile duct, may give rise to jaundice (Gould (90), Kinnicut (127), Murray (200))

Enlarged glands of the hepatic pedicle can also produce obstructive jaundice, this enlargement being the consequence of intrahepatic inflammation, malignant disease, tuberculosis, syphilis, lymphadenoma and Hodgkin's disease Jean (117), Potoschnig (215), Hubsch (114) report cases of jaundice produced by tuberculous glands of the hepatic pedicle Pepper (211) reports a case of jaundice due to compression of the hepatic pedicle by an enlarged gland in a case of Hodgkin's disease Jaundice is a common complication of carcinoma of the stomach and Fenwick (65) reports the presence of jaundice in 13 7 per cent of cases

Aneurism of the abdominal aorta near the coeliac plexus may press on the common bile duct and so cause jaundice and dilatation of the gall bladder (Dickinson (52)) *Aneurism of the hepatic artery* may compress the bile ducts above the entrance of the cystic duct (Rolland (233)) *Aneurism of the superior mesenteric artery* near its origin from the aorta has been known to compress the bile duct and give rise to jaundice (Willson (280)) Scholl (248) reports a case of jaundice due to movable *kidney* *Hepatoptosis* can also produce jaundice (Howell (113) Steele (256)) Poynder (216) reports that *ovarian tumours* can also be the cause of jaundice

Obstructive jaundice, especially when the obstruction is not complete, may last for a considerable length of time without endangering the life of the patient Wangensteen (274) reports a patient who lived for 3 years

B Non-obstructive jaundice

a Non-obstructive jaundice followed by liver cell necrosis

The essential feature of this group is that jaundice starts as a consequence of an insufficiency of the polygonal liver cells giving place to a retention of the blood bilirubin Let us for convenience make a diagram of a portion of the liver (fig 4) Normally the bilirubin which diffuses from the blood capillaries into the perivascular spaces is taken up by the polygonal liver cells and excreted into the bile canaliculi and from thence to the intestine If this excretory function of the liver cells becomes damaged to a sufficient degree, or the damage being of lesser degree, if there is associated with it an increased production

of bilirubin, some of the pigment will be retained and a condition of hyperbilirubinemia results. This bilirubin being adsorbed by the serum proteins is more or less protected from kidney excretion, and, to a certain extent, from diffusion through the blood capillaries in general As a consequence the clinical symptom of jaundice will be reached only after the hyperbilirubinemia has lasted for some days An indirect Van den Bergh reaction associated with hyperbilirubinemia and absence of bilirubin in the urine will therefore be the characteristic of this phase of non-obstructive jaundice with necrosis But the pathological process seldom stops at this phase Generally, the damage of

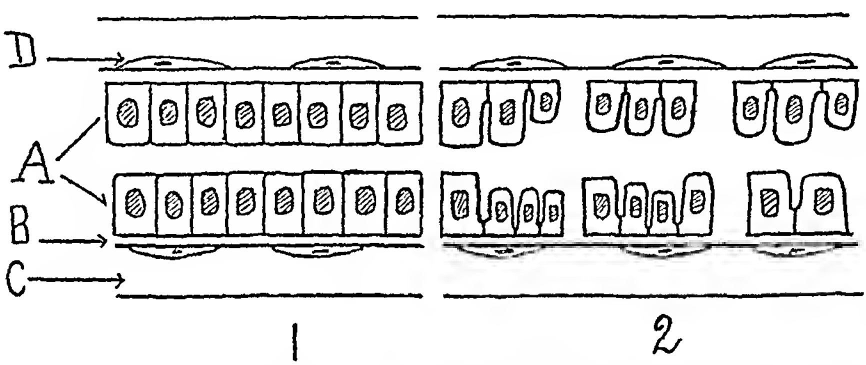


FIG 4 DIAGRAM REPRESENTING A SECTION THROUGH THE LIVER PARENCHYMA

1 Normal liver *A*, polygonal liver cells, *B*, perivascular space, *C*, blood capillary, *D*, Kupffer cell

2 Pathologic liver, showing polygonal liver cells at different stages of degeneration

the liver cell increases, and, as a consequence, some of the cells reach the final state of destruction The continuity of the bile canaliculi having been destroyed, it is obvious that some of the bile will reach the perivascular spaces and diffuse into the blood capillaries The above represents the second stage of this jaundice group, where the Van den Bergh reaction is direct, jaundice is more intense, and bilirubin is found in the urine If the body overcomes the pathological process, the liver cells regenerate, and the discontinuity of the bile canaliculi having disappeared, the Van den Bergh reaction will become indirect, remaining above the normal limits until the cells have recovered their normal function The Van den Bergh reaction in the average or severe cases of this type of non-obstructive jaundice behaves

in the same way as it does in obstructive jaundice However, there is this important difference that here the indirect Van den Bergh reaction lasts a longer time and changes into the direct type only as a consequence of cellular destruction It is in the study of this type of jaundice that Van den Bergh's contribution has been of the utmost value, not only for differential diagnosis but especially for prognosis If benign cases of this group are accompanied by an indirect Van den Bergh reaction, the transformation of the Van den Bergh reaction into the direct type will be the consequence of a severe cellular damage leading to necrosis of the polygonal cell The greater the severity of the liver cell damage, the greater will be the bilirubinemia If the inflammatory process has subsequently produced the obstruction of bile capillaries or bile ducts (cholangitis) there will also be more or less decoloration of the stools However, its distinctive feature and progress will remain invariable, as above outlined

Two main groups belong to this type of jaundice (I) infectious jaundice, (II) toxic jaundice

Infectious jaundice

The modern conceptions of the pathogenesis of infectious jaundice have been based on the researches of Chauffard, Widal and his collaborators, and it required a long time to relinquish the old classical theories based on Vichow's observations, namely, that this kind of jaundice was produced by occlusion of the bile ducts, and that the infection was of intestinal origin, being transmitted to the liver via the bile ducts It is of interest to recall that Chauffard (48) was the first to point to the insufficiency of the liver in catarrhal jaundice, this fact resulting from his experiments on alimentary glycosuria and intermittent elimination of methylene blue Whether jaundice appears as a complication in the course of a general infection or whether it is the main symptom of the malady, the course of events is the same, infectious hepatitis, damage of the liver cell, with impairment of its functions It is not until some time later, as the infection progresses, that a cholangitis develops, and the classic bile thrombi may be seen within the lumen of the bile capillaries Infectious jaundice can be divided into two groups, primary and secondary But either one or the other form will follow the same evolution

Sometimes the infection is of a benign type, and liver damage is recognized only by the presence of hyperbilirubinemia with an indirect Van den Bergh reaction, urobilinuria, absence of bilirubin in the urine and subicterus Generally the infection produces a destruction of some hepatic cells, and subsequent cholangitis, and the jaundice will become more evident with the development of a direct Van den Bergh reaction Chauffard says "en matière d'ictère infectieux, depuis l'ictère catarrhal le plus simple jusqu'à l'ictère grave le plus rapidement mortel, tous les intermediaires existent" The nature of the organism, the intensity and duration of the infection, the localization and variety of the hepatic lesions are the factors which govern the degree and character of bilirubinemia, and determine the clinical course of the disease

Primary infectious jaundice Under this group are considered those cases where the initial septicemia has attacked the liver primarily

Spirochetal jaundice, not infrequent in the United States (Sailer (242), Hayman (100)), is a very well known clinical entity since the discovery of its causal agent (*Spirocheta ictero-hemorrhagica*, by Inada and Ido) Jaundice starts 4 or 5 days after the onset of the malady, and reaches its maximal intensity 2 or 3 days later There have been no reports of the degree and quality of bilirubinemia during the first days and the only available figures are those found when jaundice is an obvious symptom

Yellow fever Generally jaundice makes its appearance on the third day of the malady but at times is recognized on the second day, or even may not be definitely present during life, or recognized only shortly before death The Van den Bergh reaction according to Klotz and Simpson (132) gives a high indirect type when performed one day before the appearance of jaundice Afterwards it becomes direct

Catarrhal jaundice A mild infectious jaundice with varied etiology, it is a common disease In numerous cases the presence of *Bacillus paratyphosus* in the blood has been reported (S Coste, Boyer and Montel (39, 40), Sacquepée (239), Frankel (80) Sarrailé (240) Cantacuzene (32)) More rarely *Bacillus typhosus* (Savy and Delachanal (241)) and *Bacillus coli* (Widal, Lemierre and Bénard (276)) have been isolated Unfortunately, in the vast majority of cases in this country, it has not been possible to isolate the germ which is the underlying cause of catarrhal jaundice

Secondary infectious jaundice Numerous infections are complicated by jaundice *Pneumonia* is frequently accompanied with hyperbilirubinemia and clinical jaundice There has been some discussion about the origin of jaundice in pneumonia Banti (10) thought that it was of hemolytic nature and in support of this theory Pollack (213), Herzfeld and Steiger (105) reported the presence of bilirubin in the sputum But as Feigl and Querner (64) pointed out, the hepatic nature of this sort of jaundice is now clear To the initial infectious hepatitis, sometimes a condition of anoxemia is added, which can precipitate or increase the jaundice Lundsgaard (157) observed a decrease in the content of the oxygen of the capillary blood in 10 to 20 per cent of patients with lobar pneumonia Hastings and coworkers (99) in 10 cases of pneumonia, found 8 in which on one or more occasions there was an arterial saturation of oxygen below 90 per cent In six cases the arterial saturation was below 85 per cent, a level of arterial saturation at which symptoms of mountain sickness may begin in normal individuals who are transferred to high altitudes (Bancroft et al (11), Monge (194)) Binger (22) in 130 patients with lobar pneumonia finds that 50 per cent of them show an oxygen saturation between 80 to 89 per cent Radvig (220) observed in a series of nine patients with lobar pneumonia, one case with direct reaction, two with biphasic reaction and four with high indirect reaction Schiff (246) reports clinical jaundice in 21 out of 826 cases of lobar pneumonia, of which only eight died, and concludes that jaundice is not of serious prognostic significance Although the presence of hyperbilirubinemia with indirect Van den Bergh reaction is of no serious prognostic significance, the writer is of the opinion that a direct Van den Bergh reaction in pneumonia must be seriously considered as it indicates an advanced hepatitis The prognosis is particularly serious when jaundice occurs during pneumonia in children

Jaundice in syphilis Early jaundice during the secondary manifestations of syphilis has often been reported, and recently O'Leary, Greene and Rowntree (208) mention one case in which the bilirubinemia, when the jaundice was already established, reached 7 9 mgm per cent, the reaction being of the direct type Late jaundice in untreated syphilis is ordinarily a result of interference with the outflow of bile by a gumma of the liver or scarring of the liver Jaundice can

follow an initial injection of arsphenamine due to the Herxheimer reaction, which is characterized by an exaggeration of the local inflammatory process

Many other infections may produce jaundice as a complication, its pathogenesis being the same as in all cases of infectious jaundice, e g, streptococcus infections (Abrami, Richet and Monod (3), scarlet fever (Meurisse (175), Izard (115)), gonoccous infectious (Raynaud, Montpellier and Boutin (222)), appendicitis (Caplesco (33)), infectious mononucleosis (Mason (169)), influenza (Crawford (42))

To give a long table indicating the degree of bilirubinemia found in the clinic in these different forms of jaundice would be superfluous When the infection is of mild nature and produces only a moderate hepatitis with slight cellular insufficiency, there will be a moderate hyperbilirubinemia, with indirect Van den Bergh reaction Clinically there will be no jaundice or a slight degree of jaundice in the mucosas, especially the conjunctiva If the infection has been more intense and as a consequence some hepatic cells have been destroyed, thus breaking the continuity of the bile channels, the jaundice will become obvious, the hyperbilirubinemia will increase, and the Van den Bergh reaction will become direct In infectious jaundice as well as in toxic jaundice all degrees of bilirubinemia are observed

Toxic jaundice

Intoxications as well as infections produce in the liver a similar series of effects resulting in the degeneration and death of the hepatic cells When the intoxication is slight the liver damage may be of so mild a nature that no clinical symptoms of jaundice are found. The liver insufficiency will be recognized only after the performance of functional tests Hyperbilirubinemia with indirect Van den Bergh reaction will be generally present When the intoxication is of more severe type, the cellular degeneration produces the destruction of more or less extended areas of liver parenchyma Jaundice, hyperbilirubinemia with direct Van den Bergh reaction will be present, the mechanism of its production being the same is in infectious jaundice Granting the same degree of cellular damage, the degree of hyperbilirubinemia will depend upon whether the toxic substances act on the liver cell alone or whether they produce at the same time an increased

destruction of red blood cells (hemolytic poisons) As non-obstructive jaundice is a function of two factors, e g, the efficiency of the liver cell and the degree of bilirubinemia, it is obvious that hyperbilirubinemia will be found if to a liver cell, slightly insufficient, but still able to excrete the bilirubin from the blood when present in normal amounts, is associated an increased red cell destruction

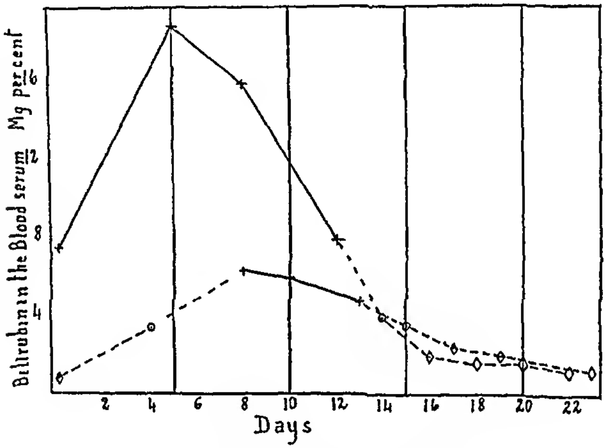


FIG 5 BILIRUBINEMIA IN ARSPHENAMINE JAUNDICE

1 Twenty days after treatment (Received at the Clinic with symptoms of jaundice)

2 Ten days after treatment

◇ ———— Indirect Van den Bergh reaction

○ = = — — Biphasic reaction

+ ———— Direct reaction

Arsphenamine jaundice Since the introduction of salvarsan and its allied compounds in the treatment of syphilis, varying degree of hepatitis have resulted from their use, which sometimes end in death This is due to the poisonous effect of the drug or of its decomposition products Isolated opinions denying the toxicity of arsphenamin (Millian (191)) are unfounded and have been contradicted by unfortunate experiences, where the death of the patient followed continua-

tion of salvarsan injections, after jaundice had appeared as a complication of treatment (Ravaut (221)) Jaundice can occur a few days after treatment (early jaundice) or several weeks after the end of a course of treatment (late jaundice) (Report of Salvarsan Committee of the Medical Research Council (173)) The earliest jaundice after salvarsan treatment has been reported by Stumpke and Bruckmann (259), who found jaundice two hours after the injection Generally, however, it is from 10 to 20 days after treatment that jaundice becomes manifest

Early jaundice is usually of a mild evanescent character and seldom severe and persistent On the other hand, late jaundice is more serious and prolonged, and may sometimes be an expression of acute yellow atrophy of the liver Gerard (83), from 370 cases of syphilis treated with arsphenamine, finds that 281 did not show hyperbilirubinemia at any time However, there was hyperbilirubinemia in 89 cases, i e, in 24 per cent of the cases Friedeman (82) states that 35 per cent of his cases showed hyperbilirubinemia

Martin and the writer,[3] studying cases of arsphenamine jaundice have found that the evolution of bilirubinemia and the Van den Bergh reaction follow the same steps as those already described as characteristic of this group of jaundice (fig 5) The first phase of hyperbilirubinemia with indirect Van den Bergh reaction can be recognized only when doing bilirubin determinations continuously and before any clinical signs of jaundice are noticed, the second and third phases (i e, biphasic and direct Van den Bergh reactions) are found as soon as clinical jaundice is present The last phase of hyperbilirubinemia with indirect reaction lasts for many days, showing evidence of the slow recovery from a complete liver efficiency

Patients with high bilirubinemia, indicating, of course, damage to the liver, should be protected from further damage by withholding salvarsan (Dixon, Campbell and Hanna (53)) The Van den Bergh reaction and bilirubin determinations must be continuously performed, not only during arsphenamine treatment, but especially before the use of the drug. When arsphenamine is administered to a patient having a bilirubinemia of about 5 mgm per liter, the use of the drug must be suspended as soon as this bilirubinemia begins to increase

[3] Unpublished observations

The toxic effect of *chloroform* on the liver cells is very well known, as it is frequently employed for experimental purposes Drury and Rous (54) found that after prolonged chloroform anesthesia there was an acute suppression of bile, as evidenced by the secretion of "white bile" from which bilirubin, cholesterol, and bile salts were absent This bile suppression was found to be due to a disturbance of the excretory power of the liver cells

Carbon tetrachloride as a specific poison of the liver cells has been reported by Lamson and his associates (142–145) The toxic effect of *phosphorous* on the liver cell is very well known Other drugs have been mentioned as capable of producing toxic jaundice, e g , atophan (Klinkert (131)), biloptin or diiodoatophan (Schwarz (250)), luminal (Neber (201)), acetylene tetrachloride (Schibler (245))

During the great war *picric acid* was used to simulate jaundice Merklen (176), Brulé, Juvillier and Baeckeroot (30) were able to demonstrate that picric acid when taken during prolonged periods can produce a toxic hepatitis, and as a consequence, a true jaundice can result

Roentgen ray irradiations can also produce toxic jaundice Cameron and Flecher (31) relate two cases, one of carcinoma of the pancreas without liver involvement, and the other of carcinoma of the pylorus, where two days after exposure to Roentgen rays, there was a rise in the bilirubinemia Case and Warthin (36) also mention the occurrence of hepatic lesions in patients treated by intensive deep Roentgen radiations

The action of *ultraviolet rays* has been studied by Pennetti (210) He exposed dogs to the action of ultraviolet rays and determined the number of red blood cells, hemoglobin and bilirubinemia He found a small increase of red blood cells and hemoglobin after the first few days, due to the stimulating action of these rays upon the hemopoietic organs and bone marrow in particular The bilirubinemia remained constant After this came a second period with diminution of red blood cells and hemoglobin, accompanied by an increase of bilirubinemia, which disappeared rapidly after suspension of treatment

Mercury has a more selective action upon the kidneys, but cases have been reported where it also produced hepatic lesions resulting in jaundice (Fiessinger (69), and Letulle, Le Noir, Oettinger (153))

In this clinic the writer has observed a case of mercury intoxication where there was a biphasic reaction with a bilirubinemia of 1 5 mgm per cent

Tetrachlorethane (employed in the fabrication of artificial pearls) when absorbed in the vapor state by inhalation, can produce jaundice (Wilcox (279), Fiessinger, Brodin and Wolf (70)) *Trinitrotoluene*, used during the war as an explosive in shells, and dinitrobenzol, are also responsible for the production of jaundice (Spilsbury, Turnbull and Stewart (255))

Among the foodstuffs capable of producing toxic jaundice, mention must be made of jaundice produced by mussels (Fiessinger and Ravina (71)), and poisonous mushrooms

Lead, toluylenediamine, and acetic acid all produce jaundice by a double mechanism To their toxic effect upon the liver cells has to be added their hemolytic action on the red blood cells As a consequence, jaundice will appear as an early symptom These cases of toxic jaundice are extremely interesting as they throw light on the pathogenesis of many cases grouped under the name of "hemolytic jaundice" Let us take acetic acid (Kaznelson (121), Landau (146)), or intoxication by lead (Lewin (155)), since both have the same form of action When one of these toxins is administered in small doses, there is first an increased destruction of red blood cells, soon followed by a slight insufficiency of the liver cells with concomitant hyperbilirubinemia Here the hyperbilirubinemia is produced by two combined factors, either of which, when separated, would not alone be able to produce bilirubin retention The Van den Bergh reaction in this case is indirect If the amount of toxin is increased, there is produced a jaundice similar to an ordinary catarrhal jaundice In both cases injury of the liver can progress to the so-called yellow atrophy Toluylenediamine jaundice has an interest because it has been widely used for experimental purposes, and its pathogenesis has been the subject of many discussions Formerly considered as a true hemolytic jaundice, today its hepatic nature is undoubted, as confirmed by Eitel's (56), and Yuasa's (287) recent investigations The nature of the jaundice produced by *phenylhydrazine* (a drug used in the treatment of polycythemia vera) has been recently investigated in Aschoff's laboratory by Alcobé (2) and Abeloff and Hummel (1) Unfortunately their

contradictory experiments cannot be regarded as conclusive and the solution of this problem requires further research It is probable, though not yet proved, that phenylhydrazine acts in the same way as toluylenediamine does, i e , by impairing the excretory function of the liver cells and at the same time, by producing, due to its hemolytic properties a sudden increase in the bilirubin formation

Cardiac jaundice The cause of jaundice in circulatory failure has been from time to time the source of discussion, owing to the difference of opinion as to whether the hepatic lesion was due to a circulatory disturbance or whether to a toxic factor, bacterial or non-bacterial Oertel (206) came to the conclusion that jaundice was not due to an hepatitis, but was most probably due to a mechanical cause in the form of chronic stasis Mallory (165), on the other hand, held that the disappearance of liver cells in chronic passive congestion was the result of bacterial necrosis Bolton (25), studying experimental venous passive congestion of the liver, came to the conclusion that the mechanical factor of stasis was the only cause in these cases Meakins (172) gives as a cause of stasis the slowing of the circulation, aggravated by anoxic-anoxemia Fischberg (76) explains this jaundice by the combination of two factors (1) injury to the liver cells by chronic passive congestion and, (2) increased destruction of red cells Eppinger (59) considers that the chief source of hyperbilirubinemia is the multiple hemorrhagic infarcts which occur so readily in the congested lungs and speaks of the similarity of the histologic picture of the spleen in chronic passive congestion and hemolytic jaundice

It is now generally agreed that chronic passive congestion which severely injures and often destroys many liver cells about the efferent veins of each lobule, is the fundamental cause of the hyperbilirubinemia present in cardiac failure Two theories have been formulated to explain its production (1) that the cells are damaged by pressure from the dammed-back blood, and, (2) that they are damaged by the deficient supply of oxygen Rich (229), in collaboration with Bumstead, observed that in pernicious and secondary anemias as well as in experimentally produced anemias, the cells about the efferent veins of each liver lobule may be damaged in a manner often indistinguishable from that accompanying chronic passive congestion, and he put forward the opinion that the damage to the liver cells in chronic passive

congestion may be referable rather to poor oxygenation than to pressure To prove the validity of this theory, it was necessary to demonstrate that anoxemia alone was able to produce an insufficiency of the bilirubin excretory power of the liver cells Resnik and Keefer (223)

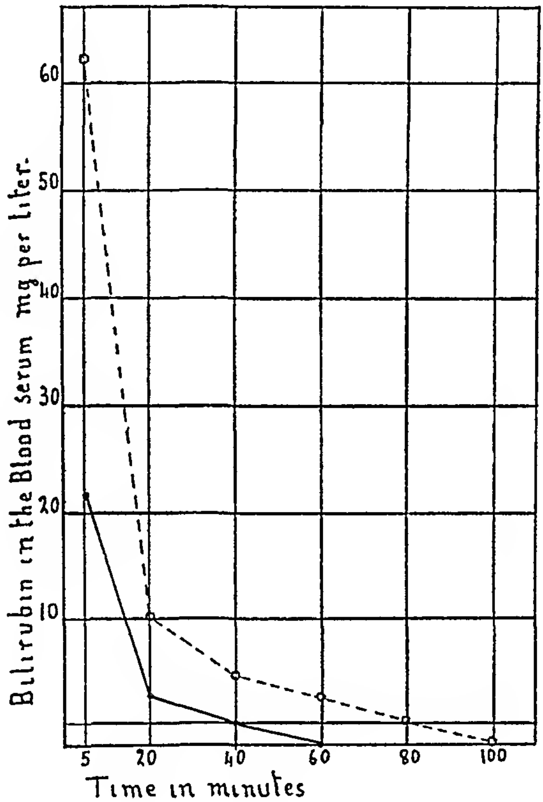


FIG 6 THE EFFECT OF ANOXEMIA ON THE BILIRUBIN EXCRETORY FUNCTION OF THE LIVER

• ———— Bilirubin excretion curve in normal dogs (average of five experiments)
o ------------ Bilirubin excretion curve in anoxemic dogs (average of five similar experiments) The dogs were kept from six to eight days in especially designed cages which contained from 6 to 10 per cent of oxygen Three milligrams of bilirubin per kilogram weight were injected intravenously The bilirubin in the blood serum was determined first five minutes after the injection, and afterwards every twenty minutes

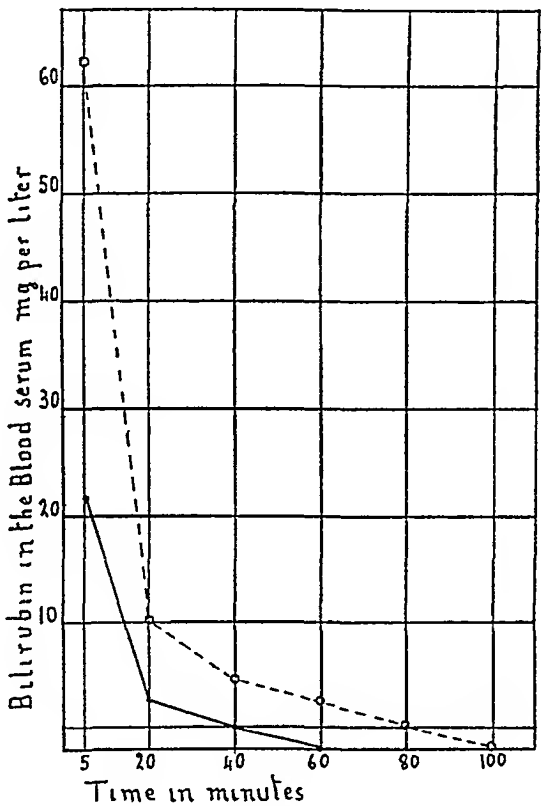
attempted to prove this theory by subjecting anesthetized dogs, previously poisoned by carbon tetrachloride (the dogs were given CCl_4 24 hours before the production of anoxemia) to short periods of anoxemia (8 to 10 hours) They reported the presence of bilirubin in the blood

serum and concluded that this bilirubinemia was caused by the action of anoxemia. It is well known, since Lamson's observations, that carbon tetrachloride alone produces bilirubinemia from 24 to 48 hours after the administration of the drug. Rich and the writer (15) have kept dogs under reduced oxygen tension (from 6 to 8 per cent oxygen content) for a period of 8 to 10 days. At the end of this period, bilirubin was injected intravenously and its concentration measured in the blood of these animals at definite intervals thereafter. The curves obtained were compared to those found under normal conditions. In anoxemic dogs there was an obvious decrease in the rate of bilirubin excretion (fig. 6) thus showing conclusively that the liver cells are very susceptible to anoxemia.

The reason for the frequency, evolution and appearance of jaundice in cardiac disease becomes thus quite clear. Anoxemia must be present over a long period in order to produce sufficient liver damage. Clinical experience obviously confirms this view, as hyperbilirubinemia, when occurring in heart disease, is present only in the chronic forms. The greater frequency of jaundice in mitral disease is also easily comprehensible. The anoxemic condition of the liver caused by chronic passive congestion, produces an insufficiency of the liver cells and gives rise to a hyperbilirubinemia with an indirect Van den Bergh reaction. This state of latent jaundice is often masked by the difficulty in recognizing the colour of the skin due to the accompanying cyanosis. When cardiac failure is complicated with infarcts of the lungs, jaundice is specially apt to occur. (Eppinger (60), Libman (156), Rich and Resnik (229) and Keefer and Resnik (126)). In this condition the pathogenesis is explained on the same basis, for the existing anoxemia has been increased, the damage to the liver cells is suddenly exaggerated, and the latent jaundice is then transformed into clinical jaundice. The Van den Bergh reaction becomes either biphasic or direct, depending on the proportion of liver cell destruction.

Cirrhosis of the liver. The degree of hyperbilirubinemia in cirrhosis of the liver depends on the extent of the chronic inflammation produced by the causal agent (toxins, infections, parasites), and the extension and distribution of the fibrous reaction. In portal cirrhosis, either of the Laennec or the hypertrophic type, the insufficiency of the liver cells, at least at the early stages, can ordinarily be discovered only

congestion may be referable rather to poor oxygenation than to pressure. To prove the validity of this theory, it was necessary to demonstrate that anoxemia alone was able to produce an insufficiency of the bilirubin excretory power of the liver cells Resnik and Keefer (223)



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that all cases of pregnancy having over 1 mgm per cent of bilirubin in the blood serum be observed carefully Hyperemesis gravidarum and eclampsia are often accompanied by jaundice, and Eufinger and Bader (63) in 20 cases of hyperemesis found 8 cases with direct Van den Bergh reaction, and in 15 cases of eclampsia observed 8 cases with direct Van den Bergh reaction All the authors agree upon the following conclusions The estimation of bilirubin in the blood serum of these patients is of great value in prognosis, since there is a parallelism between the gravity of the symptoms and the degree of bilirubinemia

b True non obstructive jaundice

The nature of true non-obstructive jaundice has been and still is the subject of much controversy Catalogued by the majority of authors under the title of "hemolytic jaundice," it was considered as due essentially to an increased red cell destruction, and overactivity of the centers where their destruction takes place It seems that these investigators, impressed only by one of the factors which enter into the production of jaundice overlooked the other factor, i e, the efficiency of the liver cell in excreting bilirubin

Rich[4] has recently pointed out that to maintain a persistent non-obstructive jaundice a combination of two factors are almost always required (1) an increased bilirubin production, and, (2) an insufficiency of the liver cells The question arises "what may cause insufficiency of the liver cells?" The experiments of Rich and the writer, previously cited, demonstrated that by the sole action of prolonged anoxemia in dogs the following phenomena resulted (1) a diminution of the ability of the liver to excrete bilirubin injected intravenously, and (2), microscopically (in dogs and guinea pigs), the production of lesions of the liver analogous to those found in pernicious anemia, hemolytic jaundice, sickle cell anemia and anemia experimentally produced in dogs by long continued hemorrhages These experiments show that the mechanism of injury to the liver cells in this type of jaundice is produced by the combination of two factors (1) The production simultaneously of hyperbilirubinemia and anemia, due to prolonged and increased destruction of erythrocytes, (2) a chronic

[4] To be published

state of anoxemia due to the anemia which injures the liver cell and diminishes its bilirubin excretory function Hyperbilirubinemia plus inefficient function of the liver cell will produce jaundice It is true that the injury resulting from this mild state of anoxemia is not sufficient to produce by itself a bilirubin retention If the amount of bilirubin elaborated by the reticulo-endothelial system does not exceed the normal limits (anemia by hemorrhage) the liver cell will still be able to excrete the pigment As soon, however, as the bilirubin production exceeds the normal limits, the liver cell will be unable to dispose of the excess and permanent hyperbilirubinemia and jaundice will follow

Malaria

Since the malarial parasites live within the red blood cells, every erythrocyte harboring the Plasmodium will be destroyed As a consequence, every attack of fever diminishes the total number of red blood cells from 5 to 10 per cent, and anemia is the immediate consequence The spleen becomes enlarged, since this organ plays an important rôle in the catabolism of destroyed erythrocytes Chauffard (46) has described a syndrome "hepato-splénique" in cases of acute malaria In these cases, splenomegaly is the first symptom to appear After treatment, the spleen reverts to its normal size, while the liver becomes congested and increases its volume

The degree of bilirubinemia in malaria depends on the clinical type of the disease, and its duration The accompanying jaundice is related to the degree of anemia, that is, the greater the anemia, the deeper the jaundice

In acute malaria there is transient hyperbilirubinemia but seldom jaundice During the attack of fever the bilirubinemia rises above its normal value Schachsuvarly (243), Russo and Serbinoff (238) find hyperbilirubinemia which reaches as high as 6 mgm per cent Kingsburg (128) in 150 cases of malaria finds that the bilirubinemia reaches an average of 0 74 mgm per cent in quartan malaria, 1 74 mgm per cent in tertian malaria, and 2 mgm per cent in tropical malaria Ross (236), from 30 cases of tertian malaria, finds hyperbilirubinemia in 29 In all of these cases the Van den Bergh reaction was of the indirect type While Arellano (9) and Kingsburg (128)

find a relation between the size of the spleen and hyperbilirubinemia, Schachsuvarly (243) denies this relationship

Special mention must be made of the behaviour of "malaria inoculata," the use of which is increasing since its introduction by Wagner von Jauregg as a therapeutic procedure in the treatment of neurosyphilis In spontaneous malaria, all authors agree as to the presence of hyperbilirubinemia with a constant indirect Van den Bergh reaction A more or less severe liver damage is often produced in malaria inoculata, as manifested by the presence of clinical jaundice with the direct Van den Bergh reaction O'Leary and his associates (208) report six cases of malaria inoculata, all showing direct Van den Bergh reactions and a bilirubinemia of from 3 mgm to 23 mgm per cent In this clinic, out of eleven cases of malaria inoculata, there was one giving a direct reaction and bilirubinemia of 6 01 mgm per cent, five giving biphasic reactions and bilirubinemia of from 2 mgm to 3 57 mgm per cent the remaining five cases behaved as spontaneous malaria (slight hyperbilirubinemia with indirect Van den Bergh) It is not at present clear just why more severe liver damage occurs in malaria inoculata than in spontaneous malaria

Blackwater fever

The considerable erythrocyte destruction occurring in this disease can produce a transient and early hyperbilirubinemia, due solely to bilirubin overproduction and inability of the normal liver cell to get rid of this excess bilirubinemia The jaundice present in this disease, however, is generally due to severe liver damage as Ross has shown Ross (236) finds the presence of a hyperbilirubinemia with the indirect type of Van den Bergh reaction when extremely mild hemoglobinuria develops When the jaundice is manifest, and hemoglobinuria severe, the Van den Bergh reaction becomes positive

Carrion's disease (Oroya fever)

This disease, caused by a blood parasite, Bartonella bacilliformis, and characterized essentially by prolonged fever and severe anemia, with a blood picture of intense regeneration, is confined to the occupants of the valleys of Peru, and presents an extremely interesting clinical picture Few other pathological entities produce so severe a

destruction of erythrocytes (Arce[5]). During the first period of the disease, called by Weiss (281) the "hematic phase," the germ affects predominantly the circulating erythrocytes. When the second period or "hystioid phase" is reached, the germ is mainly localized in the cells of the reticulo-endothelial system. In Carrion's disease, as in malaria, hyperbilirubinemia and jaundice run parallel to the degree of anemia. The Van den Bergh reaction is always of the indirect type (Guzman-Barron, A. (94)).

Icterus neonatorum

Among the many varieties of jaundice, icterus neonatorum has occupied a peculiar place for many years. Though its clinical character, its frequent occurrence and its benign course are very well known, its pathogenesis has caused considerable discussion. The question of its hepatic or hemolytic origin has been much debated. Unanimity of opinion, among pediatricians, has not yet been reached. From the considerable literature devoted to the subject one gathers the following facts.

Hyperbilirubinemia is normally present in the new born and is even present during intrauterine life, since it is found that the bilirubin content of the blood of the cord is higher than that in the blood of the arm of the infant (Hirsch (109), Yllpo (288), Schiff and Farber (252)). The Van den Bergh reaction is always indirect whether the blood be taken from the umbilical cord or from the arm (Klemperer (129), Knopfelmacher and Kohn (133), Grulu and Mebane (92), Lepehne 149)). The amount of bilirubin increases after birth, reaches its maximum between the fifth and seventh day and then subsides (Hallez (97), Mitchell (193)). This is explained in the following manner.

There is normally a polycythemia in the newborn (Lereboullet (150), Ziegelroth (290)), and an increased number of young immature nucleated red blood cells (Greil (88), Goldbloom-Gottlieb (89)), due to a chronic state of anoxemia during the intrauterine life (Ziegelroth (290)). After birth these cells are destroyed in excess as shown by the hemoglobin determinations and red blood cell counts (Williamson (283)). This red cell destruction may sometimes be accelerated either by the presence of hemolysins from the serum of the mother (observed

[5] Arce J. Clinical Lectures.

by Mitchell (193) and Lenart (147) though Goldbloom and Gottlieb (89) have not been able to confirm it), or by a marked increase in the fragility of the red corpuscles (Goldbloom and Gottlieb (89)) Jaundice is most frequent in premature, under developed infants (Lereboullet (150))

There is a functional insufficiency of the liver of the newborn due to a functional immaturity of the liver (Heynemann (107), Illpo (289)), which in some cases has been detected by using liver function tests unrelated to the bilirubin excretory power, e g , levulose test, Widal test

There are, therefore, in icterus neonatorum, the two factors which Rich regards as necessary to the production of true non-obstructive jaundice, namely, increased red cell destruction and insufficient liver cell function

Pernicious anemia

Schbeel (244) was the first to show the presence of hyperbilirubinemia in pernicious anemia, but until Van den Bergh's (269) studies, no quantitative determinations were made Van den Bergh reported an increase of bilirubinemia in pernicious anemia from four to eight times above the normal values Numerous investigators have subsequently reported the presence of hyperbilirubinemia in pernicious anemia (Eppinger (60), Botzian (26), Robertson (232)) Leaving out of account the etiology of the disease, which is still unknown, pernicious anemia belongs to the group of anemias with red cell destruction This increased red cell destruction is favoured by the extrusion into the general circulation of young immature erythrocytes condemmed to early destruction by the reticulo endothelial system There are, therefore, present in pernicious anemia the two factors necessary for the production of permanent bilirubin retention liver cell insufficiency as a consequence of longstanding anemia and over-production of bilirubin

This liver insufficiency in pernicious anemia has been indicated in studies by Harrop and the writer, (13), who have measured, in pernicious anemia patients, the bilirubin excretory function of the liver While normally the liver excretes within two to four hours the bilirubin injected intravenously (1 mgm bilirubin per kilogram of body weight), patients with pernicious anemia and *normal* bilirubinemia show a marked retention of the injected pigment (fig 7)

The amount of blood bilirubin in pernicious anemia is variable and depends on the degree of anemia and the number of young immature cells present in the blood stream In this clinic the maximum value found has been 3 mgm per cent Perkin (212) in 13 cases of pernicious anemia finds from 1 9 mgm to 0 45 mgm per cent Mosse (196) has observed a fall in bilirubinemia after splenectomy The

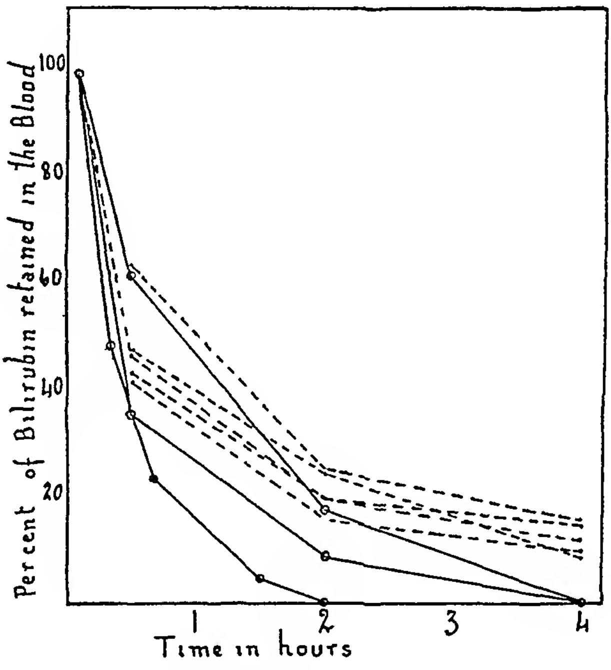

FIG 7 BILIRUBIN EXCRETION CURVE IN PERNICIOUS ANEMIA

In full lines are given the three types of normal excretion curve

In broken lines are the bilirubin excretion curves in five cases of pernicious anemia (In none of these patients was a bilirubinemia higher than 1 mgm per cent previous to the injection)

decrease of blood bilirubin with the improvement of the anemia is easily understandable in the light of what has been said concerning the adverse influence of anoxemic conditions on the function of the polygonal liver cell

Sickle cell anemia

Since this disease is one in which the anemia is produced by erythrocyte destruction, a permanent state of hyperbilirubinemia will be

reached as soon as the anoxemia resulting from anemia injures the polygonal liver cell, and impairs its bilirubin excretory power Alden (6) reports two cases with hyperbilirubinemia, and Schiff (246) made identical observations in four cases In this clinic there have been three cases of sickle cell anemia in which the blood bilirubin ranged from 1 mgm to 4 20 mgm per cent The Van den Bergh reaction is indirect as in all cases belonging to this group

Latent jaundice

When injury to the polygonal liver cell has reached the particular level which allows only a partial excretion of bilirubin, a state of hyperbilirubinemia will result without reaching clinical jaundice It is obvious that only with the detection of the blood bilirubin will the clinician be able to recognize these cases of latent jaundice All the types of jaundice belonging to the non-obstructive group associated with cell destruction will result in latent jaundice when the lesion is of benign nature, i e, when cellular destruction has not been reached The most common causes of latent jaundice are found in chronic cardiac decompensation, pneumonia and arsphenamine jaundice Short temporary obstruction of the bile duct due to gallstones can also be the cause of latent jaundice (Ta ʼ o (260)) Among this group, the cases of familial jaundice, first described by Gilbert (85) must be considered These are conditions of chronic and hereditary liver insufficiency (Manson (168)), detectable only by the permanent state of hyperbilirubinemia Diabetes is often associated with latent jaundice The presence of gallbladder disease in diabetic patients is frequent Rabinowitch (219), as well as Castle, Mullholand and Bailey (35), maintain that it plays an important etiological factor in the production of diabetes

Paroxysmal hemoglobinuria

This chronic disease, usually due to syphilitic infection, manifesting itself in paroxysms of hemoglobinuria, offers the most typical example of pure hemolytic hyperbilirubinemia The serum of patients suffering from this disease 'contains a specific hemolysin which is adsorbed by the surface of red blood cells when the temperature is lowered below 15°C During subsequent warming to body temperature the

hemolysin becomes active through the influence of the complement normally present in the blood, and hemolysis ensues. Kohler and Obermayer (135) observed a patient whose red blood cells fell 690,000 per cubic millimeter during an attack Montagnani (195) reports a case where there was a loss of two million red cells per cubic millimeter Jones (119), studying the bilirubin concentration in the blood and duodenal contents found, first a transient state of hyperbilirubinemia which reached its maximum 45 minutes after the attack, from this point the bilirubin gradually returned to normal, while the bilirubin of the duodenal content increased correspondingly

Following the more severe attacks of hemoglobinuria, a little icteric staining of the sclerae and skin is perceptible for a few days (Mackenzie (166), Barta, and Gorog (16))

Ectopic pregnancy, extravasation of blood

Whenever there is a local hemorrhage, the hemoglobin of the extravasated blood is changed into bilirubin, but the appearance of jaundice is extremely rare, as the excretory power of the liver cells is sufficient to prevent its appearance Dick (51) reported three cases of ruptured *ectopic* pregnancy with severe intraperitoneal hemorrhage, jaundice of the skin and conjunctiva and no bile in the urine Norris (205) reports two patients with ruptured ectopic pregnancies and jaundice, and states that the presence of jaundice is of great importance, and may frequently be the symptom which determines the differential diagnosis, but Horowitz and Kuttner (112) have recently denied the presence of jaundice in ectopic pregnancy, since, in fifteen cases, they did not find increased bilirubinemia

Congenital and acquired hemolytic jaundice was described for the first time by Minkowski (188), and was characterized in its essential features by Chauffard (44, 47) and by Widal and his associates (277) Hemolytic jaundice, as is well known, is characterized by hyperbilirubinemia with indirect Van den Bergh reaction, absence of bile in the urine, coloured stools, lowering of the osmotic resistance of the red blood cells against hypotonic solutions of sodium chloride, a considerable enlargement of the spleen, chronic anemia and morphologic alterations of the red blood cells Jaundice is such a dominant symptom that Chauffard has described these patients epigrammatically

as "plus ictériques que malades" The bilirubinemia is variable Botzian (26) finds figures fluctuating from 2 to 9 15 mgm per cent Kaznelson (122) reports, in one case, a bilirubinemia of 7 25 mgm per cent Schiff (246) finds from 2 5 to 7 5 mgm per cent In this clinic the values fluctuate between 2 mgm and 9 94 mgm per cent The last figure seems to be the highest bilirubinemia found in hemolytic jaundice The Van den Bergh reaction in this case was "delayed biphasic," i e, the colour reaction appeared thirty seconds after the addition of the diazo-reagent, reaching its maximum intensity several minutes later, but no bile was found in the urine It has been said that a solution of bilirubin added to normal serum gives an indirect reaction, until a certain concentration is reached (16 mgm per cent) beyond which the reaction becomes direct It is therefore, possible, though probably extremely rare, to observe cases of hemolytic jaundice giving biphasic Van den Bergh reactions If the amount of bilirubin exceeds the saturation point, or, the bilirubinemia being not so high, if the concentration of serum protein is lowered, theoretically a change in the Van den Bergh reaction may appear

The disappearance of jaundice observed in cases of congenital hemolytic jaundice after splenectomy, has been confirmed through bilirubin determinations before and after splenectomy by several investigators (Rich and Rienhoff (228), Schiff (246)) Sometimes, after splenectomy, there is a change in the Van den Bergh reaction A case of this nature was observed in this clinic A patient with hemolytic jaundice (indirect Van den Bergh reaction, bilirubinemia, 8 34 mgm per cent) was splenectomized The day following the splenectomy, the Van den Bergh reaction became biphasic, and the bilirubinemia dropped to 3 76 mgm per cent Some days later the Van den Bergh reaction became indirect with a bilirubinemia of 1 mgm per cent That the spleen takes a considerable part in the overproduction of bilirubin has been demonstrated by Kaznelson (122), Eppinger (60) and others, who found more bilirubin in the splenic vein than in the peripheral circulation

Although the excellent results obtained by splenectomy in cases of congenital hemolytic jaundice seem to favor Minkowski's first observation that this is primarily a disease of the spleen, the persistence, in some cases, of the diminished osmotic resistance of the red blood cells after splenectomy complicates this interpretation

In *acquired hemolytic jaundice* splenomegaly is the consequence and not the cause of the hyperbilirubinemia, as the inconstant results produced by splenectomy seem to prove

Widal and his associates consider that the primary cause of hemolytic jaundice is the alteration of the red blood cells due to hemolysins fixed on their surface, which renders them more susceptible to destruction These hemolysins may be either of exogenous or endogenous origin The presence of hemolysins in the pathologic spleen has not as yet been demonstrated In four cases of splenectomy for hemolytic jaundice, those of Vaquez and Giroux (271), Antonelli (8) and two of Kahn (120), hemolysins have not been demonstrated. The following questions present themselves for analysis

Is hemolytic jaundice of strictly hemolytic nature? Is there only overproduction of bilirubin without any hepatic lesion? Widal and his associates deny any participation of the liver cell since the carbohydrate tolerance test, and the Widal test have been negative in cases studied by them But how is it possible to draw conclusions about the functional efficiency of the bilirubin excretory power of the liver cell from the results of tests which measure quite different functions? Can there not be isolated dysfunction? The existence of such states in liver pathology is beyond doubt

The production of a liver lesion by the action of uncomplicated anoxemia, a lesion which produces a delayed excretion of bilirubin injected intravenously and the presence of this same disturbance in pernicious anemia, strongly suggests similar functional impairment of the liver cell in hemolytic jaundice, especially in its late stages, when anemia is always evident

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NEPHROSIS

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CONTENTS

INTRODUCTION

"Nephrosis" began its existence in medical nomenclature as a point of view The original views of Virchow in regard to parenchymatous inflammation proved inadequate and were replaced by the concepts of exudation and proliferation in the vascular and supporting systems This made it desirable to have a general term for these changes in renal epithelium so commonly found but not properly belonging under the term "nephritis" which connotes "inflammation of the kidney" It was Friedrich Muller (1) who first saw the opportunity of clarifying the situation and in 1905 suggested the term "nephrosis" for the purely degenerative conditions of the kidney, meaning, presumably, although not expressly stating it at that time, the tubular nephropathies, and not the equally degenerative vascular changes of arterio- and arteriolosclerosis Friedrich Muller realized the difficulty of absolutely distinguishing, in some instances, between purely degenerative and partly inflammatory renal diseases even in morphological

studies Hence he was justly conservative in making no claims for clinical differentiation, although he had the possibility clearly in mind "Nephrosis," therefore, was for the time being largely an anatomical term

In less than ten years after its introduction the term "nephrosis" was to take the German medical world by storm and this time on a bold clinical footing with a solid pathological background As one of the trinity of Volhard and Fahr's (2) classical division of bilateral hematogenous, renal disease—nephrosis, nephritis and nephrosclerosis—it became rapidly popular among most German clinicians, while stirring up a host of antagonists in the camp of pathologists A few years later, nephrosis made its appearance in the United States as "Epstein's nephrosis," was translated on a somewhat shaky basis to Great Britain where it has only recently achieved any real recognition, and invaded France on occasions without making any serious impression upon the physiological classification of renal diseases prevailing there Somewhat before the publication of Volhard and Fahr's monograph in 1914, Munk (3) established the unique significance of "lipoid degeneration" in the kidneys and the presence of doubly refractile lipoid droplets in the urinary sediments of patients with "chronic parenchymatous nephritis" especially on a luetic basis He quickly adopted the term "nephrosis," prefixing the word "lipoid," and thus gave the name "lipoid nephrosis" to the class of patients under discussion—a name that was far more accurately descriptive than any hitherto proposed With Munk (4) the disease spread beyond the organic confines of the kidneys to become a general constitutional disturbance of all the colloids of the body His views were widely accepted Epstein (5) took a less mysterious, rather more logical, view of the situation, particularly in regard to nephrotic edema He reverted to Starling's (6) pioneer work on the rôle of the colloid osmotic pressure of the serum proteins in the exchange of fluids between the vascular and tissue spaces in normal and edematous states, and built up a superstructure of fact and theory which will be considered in detail later These developments in our knowledge of nephrosis came rather rapidly, thanks to the enormously stimulating effect of the new classification and terminology upon the morphological, clinical and biochemical studies of renal disease

From 1905 to the present, there has been a considerable evolution in the meaning of "nephrosis," particularly on the clinical side The tendency has been to restrict the name to a much narrower and more clearly defined group of cases This change in content has been criticized by its opponents as indicating lack of unanimity and absence of a clear conception in regard to the disease It seems to the reviewer that the present restricted significance of "nephrosis" is a desirable state of affairs and indicative of increasing clarity rather than confusion in the nosology of renal diseases It will be the purpose of this review to indicate the evidence in favor of the existence of a definite clinical and pathological "entity" known as nephrosis ("lipoid," "genuine," etc), to compare it with the "nephrotic syndrome" in chronic glomerulonephritis and amyloidosis, to point out the manifold relationships of the disease to problems in pathological physiology and above all to emphasize the defects in our knowledge concerning these problems Considered from this point of view, the question as to the existence or non existence of a "pure nephrosis" becomes vastly secondary to the acquisition of more facts and better theories concerning albuminuria, the formation and persistence of edema, the metabolism and deposition of lipoids in the tissues, and the true rôle of the kidneys in certain forms of so-called Bright's disease To the historically minded clinician or pathologist it will occur that exactly similar problems confronted Bright (7) and that it has taken a hundred years to establish more definitely some of the facts and theories that he so modestly brought forward

A few words are necessary in regard to the objections of some pathologists to the term "nephrosis" Aschoff (8) and others have objected to its etymological significance—"full of kidney" As F Müller (9) pointed out in 1916 this objection is invalidated by the established usage of "osmosis," cirrhosis," "phimosis," etc Aschoff's own substitute "nephropathy" is objectionable because it has both a general and a particular meaning Another name given by Aschoff (8) was "nephrodystrophy" This took with Lowenthal (10) who turned it into "lipoid nephrodystrophy" It is not surprising that "nephrosis" or "lipoid nephrosis" was not rapidly displaced by these equivalents The repeated attempts of Aschoff and others to raise the question of "tubular nephritis" versus "tubular degeneration"

have led to no useful results inasmuch as inflammation is largely what one defines it to be, and to those who have accepted Lubarsch's definition, the concept of "tubular nephritis" becomes partly a philosophical point of view rather than one of morphology It seems at the present writing that "nephrosis," with or without some qualifying adjective, has come to stay and represents good medical usage, when properly defined and delimited

WHAT "NEPHROSIS" DOES NOT INCLUDE

As used in this review "nephrosis" does not include a variety of anatomical and clinical conditions that, at one time or another, have all been subsumed under that heading The simple albuminurias and cylindrurias of febrile conditions and metabolic diseases, the more severe forms of renal disease produced by various metallic and other poisons, the specific nephropathy of pregnancy which in its marked albuminuria and edema bears a superficial resemblance to nephrosis—all of these have nothing truly in common with the specific clinical and pathological condition designated in this review as "nephrosis," and will therefore be left out of the picture Volhard, Fahr, Munk, F Muller and Epstein while at first using "nephrosis" in its more general and anatomical sense have all admitted the uniqueness of the disease "nephrosis" in its limited sense

DEFINITION OF NEPHROSIS

What do we mean by "nephrosis?" It is a rare chronic disease of children and young adults, usually insidious in its onset and without any definite relationship to infectious diseases in most cases although in some the condition seems to follow chilling, upper respiratory infections, or active lues The underlying cause is not known The clinical features are both positive and negative, the latter as important as the former Among the positive findings are subcutaneous edema and fluid in serous cavities, albuminuria, oliguria, waxy pallor, typical urinary sediment, good renal concentrating ability, decreased protein and increased lipoid content of the plasma or serum and decreased basal metabolic rate The negative or absent findings are hematuria, increased blood pressure, cardiac hypertrophy or enlargement, abnormal peripheral or retinal arteriosclerosis for the age of the individual,

renal insufficiency and true uremia The course is typically chronic, with remissions during which all of the signs and symptoms, with the exception of albuminuria, may disappear Complete recovery may occur after months or years of a checkered course of ups and downs Often, however, the general state of the patient is such as to predispose him to various acute and chronic infections, particularly pneumococcal in origin, the outcome of which is very likely to be fatal The pathology of nephrosis is at present limited to the kidneys, in which tubular degeneration of a characteristic type is found in the absence of any significant or primary glomerular or vascular changes, with the processes of parenchymal atrophy, cirrhosis and contraction occurring very exceptionally, if at all, in the uncomplicated type The morphologic picture thus distinguishes nephrosis from any other type of renal disease, especially from chronic glomerulonephritis which may, at some stage in its course, produce a strikingly similar clinical picture The pure, uncomplicated type of nephrosis is rare at autopsy Very frequently, there exists in addition a mild chronic glomerulonephritis which has been overlooked clinically Less commonly amyloidosis is found, especially in those patients in whom the clinical picture of nephrosis has developed during the course of one of the forms of chronic suppuration or cachexia ordinarily responsible for general amyloidosis It is felt by the reviewer that a more critical clinical study of patients with suspected nephrosis would result in fewer incorrect diagnoses and disappointing pathological findings, and a firmer establishment of the existence of pure nephrosis As ordinarily made, the clinical diagnosis of "pure nephrosis" very often means, at autopsy, a mild chronic glomerulonephritis of the nephrotic type

CLINICAL DESCRIPTION IN DETAIL

a Incidence The disease is very rare, even clinically, in the pure uncomplicated form Epstein (11) claims to have had an unusually large experience but does not give sufficiently detailed statements or case reports in his articles to allow accurate conclusions to be drawn Schlayer (12) found only 6 cases of nephrosis among 300 cases of Bright's disease and in one or two of the six there was some doubt as to the diagnosis Eppinger (13) mentions only 4 cases of pure nephrosis in "many thousand" cases of renal disease Kollert (14) also

points to the extreme rarity of the pure disease Naturally, the incidence at autopsy becomes even more vanishing Fahr (15), who has had the largest experience of any pathologist in this field, required twelve years to obtain 8 autopsies that could withstand the withering criticism of experienced opponents like Lohlein and Aschoff Bell and Hartzell (16) had no case of nephrosis in their excellent review of 69 cases of glomerulonephritis among 3300 consecutive routine postmortem examinations McElroy (17) reports one uncomplicated case at autopsy out of a clinical study of 600 patients with Bright's disease, of whom 19 are considered as having "lipoid nephrosis" In short the clinical incidence of nephrosis is somewhere between 1 and 5 per cent of all patients with bilateral, non-suppurative renal disease Any reports of a much higher incidence are to be regarded with suspicion Richard Bright himself probably never saw a case of nephrosis, as judged from his published case reports (7) (18) and the statement of Aschoff (19) Weigert, according to Volhard (20), hunted all his life for a pure degenerative type of renal disease, without success

b *Age and sex distribution* It is difficult to give accurate information concerning the age distribution of patients with nephrosis because of the uncertainty in regard to the diagnosis clinically In general, however, practically all of the cases have occurred in children and young adults The autopsy material bears this out, there being only one patient over 40 years old (age 53), one in the fourth decade, seven in the third, eight in the second and nine in the first decade in a total of 26 cases published by various authors While this is too small a series from which to draw statistical conclusions, it probably represents a fair approximation to the actual frequency in various age groups In regard to sex and race there is no striking difference apparent

c *Etiology The actual cause of the disease is entirely unknown* The pathogenesis of nephrosis will be taken up in considerable detail later on In the earlier reports various infectious diseases were listed as causes of nephrosis, the assumption being that the bacterial agent or toxin responsible for the manifestations of the infectious disease was also directly to blame for the development of nephrosis This point of view has lost ground, however, and it is fairly generally conceded now that infectious diseases play only the rôle of the immediate excit-

ing factor on a soil already prepared The disease that above all others seems to act in this way is syphilis in the active secondary stage A good description of such cases was included in an address by Bradford in 1907 (21)

Munk (3) reported 14 cases occurring during active or partially treated lues Patients with this type of nephrosis are found in the older literature under the heading of acute syphilitic nephritis, often blamed upon the particular therapy in course at the time of the onset of edema and albuminuria A classical report was that of Javal (22) whose patient had massive edema and ascites, with marked albuminuria, for almost a year, the onset occurring eleven months after a hard chancre and during the course of mercurial treatment Stengel and Austin (23) were probably the first in the United States to demonstrate doubly refractile lipoids in the urine of such patients Burgerhout (24) detailed 5 interesting cases of luetic nephrosis but stated that lues is only a predisposing factor It may be significant to note that erythrocytes, though not in large numbers, are usually found in the urines of these patients, especially when the onset is rather acute One wonders if some cases do not actually represent an acute glomerulonephritis with marked nephrotic tendency However, purely degenerative forms undoubtedly occur in syphilitic patients, as emphasized by Wohlwill (25)

Volhard and Fahr (2) listed 36 cases of "chronic nephrosis" Of these, 18 were ascribed to tuberculosis (bones and lymph glands) 5 to lues, 5 to chronic suppuration (osteomyelitis, etc) and one to sarcoma, while 7 were classed as pure or "genuine" nephrosis of unknown origin In this series amyloidosis of the kidney combined with lipoid degeneration accounts for the predominance of tuberculosis and other chronic suppuration as apparent etiological factors Of this group only the 7 "genuine" cases and some of the luetic cases should be included under nephrosis as previously defined Munk (3) (4) (26), has consistently regarded the nephrotic syndrome in tuberculosis as secondary to amyloidosis and not a true, primary nephrosis A similar opinion has been expressed by Epstein (27) In the cases of nephrosis unassociated with conditions known to result in amyloidosis, no amyloid is ever found in the kidneys This would make it seem very unlikely that the amyloid deposition occurs in the advanced

stages of nephrosis as a secondary phenomenon The problem of the relationship between the two pathological processes in the kidneys will be taken up again later on

It is interesting that in Volhard's series mentioned above syphilis was credited with only about 14 per cent of the cases In his book on renal diseases (28), Strauss states that syphilis is found in only 25 per cent of patients with lipoid nephrosis Munk no longer attaches to lues the importance that he did in his early publications but still considers the virus of syphilis as the only one known to produce lipoid nephrosis Epstein (11) gives lues a very minor rôle in nephrosis Most other authors agree with him The factor of coincidence has not been sufficiently considered

By far the largest proportion of the cases of nephrosis falls, therefore, into the group of "*unknown etiology*" This is simply a restatement of the first sentence in this section of the review The rôle of general constitutional factors, undernutrition, chronic pallor, and environmental factors such as poverty and its attendants, has been stressed by virtually all writers on the subject of nephrosis Similar conditions however are often listed as predisposing factors in many other diseases Hence one can only conclude that the constitutionally or environmentally unfavored individuals are very likely to develop one disease or another

d Edema Without edema there is no nephrosis Edema is the symptom that brings the patient to the physician Edema is the physician's greatest stumbling block in the treatment of this disease Infection of edema or ascitic fluid usually brings the patient to autopsy This edema may develop very rapidly, as it does in some luetic patients, but usually it appears insidiously, either spreading slowly and progressively or coming and going at first, as does an early cardiac edema It resembles the latter in the beginning, being essentially a dependent type of edema, first involving the feet and ankles, then the legs, the inner aspect of the thighs, the scrotum or labia, transforming the lower extremities into shapeless, dead-white trunks more or less useless to the patient because of their weight However, unlike cardiac edema, the face is early affected with variable swelling of the eye-lids, the cheeks, the parotid region and the boundary between the lower jaw and the neck This is most apparent in the morning after a night's

sleep in the recumbent position A waxy-white pallor of the swollen face with bluish-white eye-lids gives the patient a pathognomonic appearance, especially when the skin is delicate, as is often the case The edema shifts with position Hence, the bed-ridden patient will have pads under the thighs and over the lower back, while early in the morning the face may resemble unilateral mumps on the side that was dependent during the night The backs of the hands, the fore-arms and arms, the abdominal and thoracic walls and even the scalp may share in the edema when it is extreme In most patients, however, the lower half of the body is chiefly affected in addition to the face Ascites is present to some degree in all cases and may persist long after external edema has subsided Hydrothorax is common Pulmonary edema of a moderate degree is found in the severe cases but is rarely alarming Edema of the larynx or epiglottis is very unusual Edema of the brain is diagnosed more often than proved and is to be suspected only in cases with excessive anasarca and especially severe involvement of the head and neck Repeated coma during severe edema with terminal fatal convulsions were reported by Murphy and Warfield (29) Edema of the optic nerve head has not been reported The frequent, watery bowel-movements observed during the rapid development of general anasarca and ascites, or at the height of a stationary dropsy, have been ascribed to edema of the intestinal mucosa Similar changes in the stomach may partly explain the nausea and vomiting during such states

The extent and amount of edema vary considerably from patient to patient The stubborn persistence, however, and the lack of response to the usual diuretic measures are extremely characteristic of nephrotic edema For weeks and months the patient may be swollen to a forlorn degree and the skin of the legs, external genitalia, or abdominal wall be actually bursting and oozing, yet no change for the better take place Then suddenly, when the situation seems darkest, a flood of diuresis may set in and wash the patient out to his true form, usually skin and bones Therapeutic enthusiasm may be brilliantly rewarded if some form of therapy happens to have preceded nature's action Where this is not the case one can only marvel and speculate at the sudden turn However, undue optimism at such a time is liable to be unwarranted for very soon, following a cold or other slight change

in the patient's general health, a relapse may set in and the whole process wind its discouraging way again Excellent descriptions of these clinical events are found in Volhard's monograph (20) and in Munk's book (26)

The edema and fluid in serous cavities may persist for weeks, months or years with remissions of varying degree and equally irregular relapses. Of the factors which may tend to increase the amount of transudation the salt and water intake are undoubtedly the most important from the point of view of controllability Various upper respiratory infections, including inflammation of the nasal accessory sinuses, may have a temporary aggravating effect On the other hand, there are a number of instances in the literature where fairly severe intercurrent diseases such as erysipelas, lobar pneumonia, etc have been associated with or closely followed by a critical disappearance of transudates down to the last traces In one reported case, that of Karácsony (30) massive edema disappeared on two occasions immediately after the crisis of lobar pneumonia, when, previously, no measures had any effect Aldrich (31) has published very interesting material in regard to the course of nephrotic edema in children, particularly as modified by infections

e Albuminuria If there is no nephrosis without edema, there is equally *no nephrotic edema in nephrosis without albuminuria* It is very likely, though difficult of actual proof in most cases, that albuminuria usually precedes edema, sometimes at a long interval This is certainly true in the luetic cases where urinary examinations are carried out during the course of anti-luetic regimes Most evident is the fact that albuminuria often persists after edema and ascites have vanished and furnishes the only warning of a possible relapse When albuminuria itself clears up and does not return over a period of months, one may begin to look forward to a possible recovery In the absence of all symptoms other than a persistent albuminuria of considerable degree, a bout of edema is to be considered as somewhere in the offing

While the concentration and daily amount of protein in the urine vary considerably, they are always markedly elevated in the active edematous stages of nephrosis and often reach values rarely seen in other types of renal disease Thus, concentrations of 5 to 20 or 30

grams per liter are quite common and values up to 60 grams per liter have been reported The higher concentrations are naturally observed in association with marked edema and oliguria The actual output per day may vary from 5 to 50 grams of protein, the amount varying roughly with the severity of the transudation During marked diuresis the concentration naturally drops to 1 or 2 grams per liter or even less, while the output may still total 5 grams or more In the edema-free stages of nephrosis, albuminuria may diminish to a trace or disappear entirely for a while, to return with a relapse In some cases slight albuminuria persists for years without affecting the general health The composition of the urinary proteins and the relationship of albuminuria to edema and other features of nephrosis will be detailed later

f Other urinary changes The urine varies with the stage of the disease and the presence or absence of edema Typically it is scanty—500 cc or less in 24 hours—dirty-brown and turbid, often with a heavy sediment settling out on standing It is usually acid in reaction when passed but tends to decompose rapidly and to turn alkaline and foul smelling The specific gravity is high in proportion to the 24 hour output, 1020 to 1040 or even 1060 (32) depending, of course, upon the volume and the concentration of protein and other solids The chloride output is usually negligible in patients with increasing edema, but may approach the intake of chloride after edema has reached a stationary level Anuria does not occur even with extreme degrees of edema (20)

Gross hematuria never occurs in pure nephrosis

The *sediment*, during the active stage of the disease, usually is rich in casts of the hyaline, granular and epithelial variety The first are as a rule the most numerous and likely to occur even when no other forms are present Many renal epithelial cells may be found at times A variable number of leucocytes is present but there are *no erythrocytes* By "no erythrocytes" is meant the absence on repeated examinations of more than an occasional red blood cell in a high power field of a centrifuged specimen In other words, erythrocytes should not be found in larger numbers or with greater regularity than in supposedly normal urines Any deviation from this criterion should be investigated seriously as it may spell the difference in diagnosis between

nephrotic glomerulonephritis and nephrosis In such instances, the quantitative method for the examination of the urinary sediment developed by Addis (33) may prove of value It is also wise to carry out a chemical test for blood on the sediment in view of the possibility of rapid hemolysis in alkaline urines Aldrich (34) discards the diagnosis of nephrosis if positive benzidine tests are obtained

During the edematous, oliguric stages of nephrosis there are usually present either as free droplets in the urine or as highly refractile droplets in epithelial cells, in leucocytes, and especially in granular "fatty" casts ("compound granular casts"), *doubly refracting lipoid* spherules as determined by the aid of the polarizing microscope In the dark field of this microscope they appear as bright Maltese crosses with dark cross-lines, the axes rotating with rotation of one of the Nicol prisms When these droplets are superimposed, packed together or very small, the individual crosses cannot be made out with the ordinary magnification and the entire mass presents a silvery gray luminescence on the dark background These droplets may be present one day and absent the next They may be seen in every field in some sediments, filling up large cells, presumably swollen renal or phagocytic cells In other instances only a most careful search will reveal a typical droplet or two With experience one large droplet is sufficient for recognition of their presence It must be remembered, however, that they may at times originate in other parts of the genito-urinary tract (bladder, prostate, etc) than the kidneys Criteria by which they may be distinguished from other urinary crystals, foreign particles, etc have been clearly laid down by Kaiserling and Orgler (35), the original discoverers of this phenomenon in relation to medicine, by Munk (3), who first connected their presence in the urine with the existence of lipoid nephrosis and by Genck (36) who examined a very large number of urines representing renal and other diseases and described in excellent detail the differential points between doubly refracting lipoids, confusing crystals and other structures During diuresis and in the edema-free stages of nephrosis there are often no such lipoid droplets to be found and the urinary sediment may show only a few hyaline casts or nothing at all unusual Ordinary fatty droplets, staining well with Sudan III or IV, may be found in cells and casts with or without the droplets showing double refraction, and they

are not peculiar to the nephrotic syndrome since they may occur in a great variety of conditions associated with simple fatty degeneration or infiltration of the kidneys, as in hyperthyroidism, diabetic ketosis, phosphorus, chloroform and ether poisoning, and pernicious anemia According to Munk (26), the doubly refractile lipoid droplets are not found in the urine in diseases other than nephrosis, the nephrotic forms of glomerulonephritis, amyloid disease of the kidneys with lipoid degeneration and rarely arteriosclerotic renal disease

g *The cardiovascular system* It is a striking phenomenon, indeed, that in patients presenting the other features of what, at first glance, one would consider a serious form of Bright's disease, symptoms and signs referable to the heart and vessels should be so conspicuously absent as to furnish an extremely important negative criterion in the diagnosis of nephrosis Neither early nor late in the clinical course of uncomplicated nephrosis is an increase in blood pressure ever found In fact many of the patients are likely to have hypotonia for long periods of time The heart, correspondingly, shows no clinical evidence of enlargement nor of the other abnormalities so commonly present in other forms of diffuse renal disease A cardiac element in the edema of nephrosis is practically unknown, in contrast to the situation in certain stages of glomerulonephritis and arteriosclerotic renal disease In the absence of any hypertension and in the young age-groups ordinarily affected by nephrosis it is not surprising to find completely soft and pliable peripheral arteries Furthermore, examination of the eye grounds adds only negative information, namely, absence of any evidence of retinal arteriosclerosis and of neuroretinitis albuminurica, so-called, freedom from hemorrhages, edema, lipoid deposits and any of the other features that make it possible for an ophthalmologist to diagnose "renal disease" Subjective changes in vision may occur in those patients with rapidly developing edema and in whom cerebral edema is suspected Actual objective findings have not been described The development of hypertension and the changes associated with it in the cardiovascular system may, of course, occur theoretically in those individuals with nephrosis who have reached the age ordinarily affected by vascular diseases A complicated clinical picture would result, the elucidation of which would be virtually impossible unless the entire history of both conditions were

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by Volhard (20) and others and used as evidence in favor of the non-renal, non-retention theory of nephrotic edema In general, the uncomplicated case shows no significant changes in the cellular elements of the blood Temporary variations may occur during rapid clearing of edema and the associated dilution of the blood Where true anemia exists, it is of the secondary type and has often preceded the onset of nephrosis It is not unlikely that nutritional anemias may be brought on by improper diets maintained over long period of time during the edematous and albuminuric states Much more knowledge is necessary in this field The leucocyte count and the differential picture are not of significance in nephrosis except in heralding the approach or existence of some one or other of the intercurrent infections that may be of such dangerous import to the patient The plasma or serum is often opalescent, milky or creamy in the fasting period There is no tendency for a separation into layers In addition the fluid part of the blood is liable to be thin and watery due to its low protein content The coagulation time is not characteristically affected, nor is the bleeding time The clots retract well The sedimentation rate, as might be expected from the physical properties of the blood in active nephrosis, is markedly increased

The chemical composition of the blood in uncomplicated nephrosis presents striking deviations from the normal in the protein and lipoid elements These will be discussed in separate sections In regard to the *non-protein nitrogenous substances*, they are uniformly within normal limits except under definite modifying conditions, namely, marked oliguria and sudden increase of edema (especially in children) when not enough urinary water may be available to carry off nitrogenous waste-products in spite of excellent renal function, or in rapid disappearance of edema fluid (containing approximately the same concentration of non-protein nitrogen as the blood) when there may be a relative lag in the excretion rate of the nitrogenous substances in comparison with that for water and salts, or during the course of high protein diet therapy, fever or any other condition causing an increase in protein catabolism In all of these a moderate elevation in the non-protein nitrogen of the blood may be apparent, but tests for renal concentrating ability will show excellent function and thus rule out a renal insufficiency Furthermore, such apparent retention is a tem-

porary phenomenon In nephrosis the distribution of nitrogenous waste-products in the edema fluid is no more a protective mechanism against uremia than the glucose content of the same edema fluid is a prophylactic measure against hyperglycemia and glycosuria

The *chloride* content of the blood in nephrosis may be normal, high or somewhat decreased, depending upon the intake, the state of edema or diuresis and therapeutic factors Considering the enormous amount of work done upon blood chlorides since the time of Widal's explanation of renal edema as due to salt retention by an inefficient kidney, relatively little has been learned The radical differences in the chloride content of whole blood and serum, or plasma, have not been sufficiently taken into account The effect of anemia in increasing the chloride content of whole blood, because of greater plasma volume, has often not been controlled In general, the serum chloride tends to be slightly elevated during the edematous stage

The *calcium* concentration of the serum falls with the proteins in a roughly parallel fashion, as pointed out by Salvesen and Linder (37) and recently confirmed by Peters and Eiserson (38) Values as low as 7 mgm per 100 cc may be reached but tetanic manifestations do not occur, presumably because the reduction is chiefly in the non-diffusible fraction related to the plasma proteins As the proteins increase, with decrease in albuminuria, the serum calcium rises toward a normal level

Other serum electrolytes, such as sodium, potassium, magnesium, phosphate, bicarbonate and hydrogen ion are not significantly affected in nephrosis, indicating a normal acid-base balance, another evidence of normal renal function Analyses have been reported by Salvesen and Linder (37), Linder (39), Salvesen (40), and Blackfan and Hamilton (41) The last authors found decreased total base in some cases but considered this secondary to the albuminuria and low serum proteins On the whole, the changes are those expected from the diminished protein content of the blood The reaction of nephrotic patients to the administration of acid-forming diuretics has been shown to be essentially normal by Keith, Barrier and Whelan (42) (43), Van Slyke and his associates (44), Linder (39) and Salvesen (40)

The volume of the circulating blood in nephrosis has been determined by the various dye methods Linder, Lundsgaard, Van Slyke and

Stillman (45) found a normal plasma volume in typical nephrosis which was quite constant during edema and diuresis There was no evidence whatsoever in their results for the existence of a "hydremic plethora" Brown and Rowntree (46) described a "normovolemia" in nephrosis, in contrast to "hypervolemia" in cardiac edema and "oligocythemic hypovolemia" (true anemia) in glomerulonephritis They observed no fixed relationship between the water content of the plasma and the volume state During the disappearance of renal edema by diuresis, only minor fluctuations in plasma volume were noted In a more recent paper the same authors (47) again reported a normal blood and plasma volume in non-anemic cases of nephrosis, but an "oligocythemic hypervolemia," with a 20 per cent excess of plasma volume in anemic cases During and after diuresis no significant changes took place, indicating that the findings were not due to simple dilution of the blood The dye used was Congo red, a somewhat unfortunate choice since Bennhold (48) had shown that in cases of nephrosis the dye disappeared from the serum to the extent of 32 to 60 per cent (about three times the normal rate) between 4 and 60 minutes after intravenous injection of a given amount Furthermore, early excretion of the dye in the urine occurred, which is not the case in normals This, incidentally, is evidence of increased permeability of the renal capillaries to colloids Seyderhelm and Lampe (49) confirmed this observation and found that trypan-red and trypan-blue were also readily excreted by the nephrotic kidney The edema fluid of these patients showed no staining with the dyes Later Bennhold (50) concluded from experiments in vitro that in nephrosis the rapid exit of dye from the blood was due to decreased adsorption capacity of the plasma proteins, consequent upon their low concentration and the shift toward the globulin fraction Just what effect Bennhold's discovery has on the interpretation of plasma volume estimation in nephrosis is uncertain, since in the dye methods the last sample of blood is drawn only 3 minutes after injection However, some caution must be exercised in drawing conclusions from the Congo red method

) The transudates Edema fluid obtained from the subcutaneous tissues is usually water-clear and limpid in thin layers or opalescent in thicker layers Because of the negligible protein content, the specific gravity is extremely low, being always below 1 010 (20) Ascitic

and pleural fluids show a characteristic "soap-water" appearance, often called "pseudo-chylous" This is similar to the appearance of water to which a few drops of milk have been added Even after centrifuging at high speed to get rid of suspended endothelial cells, etc, the same opalescence or "lactescence" persists The specific gravity is usually below 1 010, often down to 1 004 or 1 005, figures lower than those found in any other type of transudate Quantitative chemical data will be given later

k Renal function So far as can be determined by the various methods employed in testing renal function, there is no impairment in typical uncomplicated cases of nephrosis except that decreased water excretion occurs and may lead to an oliguria sufficient by itself to produce temporary increase in the non-protein nitrogenous constituents of the blood This decreased water excretion is seen only in patients with increasing or persistent edema and is according to Volhard (20) of extra-renal origin, inasmuch as intravenous injections of saline solutions may still lead to an adequate diuretic response. However, water taken by mouth does not produce the usual rapid diuresis in active nephrosis so that the dilution test for renal function as devised by Volhard (20) gives very poor results This is only an apparent defect, due to non-renal causes, just as inability to excrete a urine with high specific gravity in the concentration test of Volhard (20) does not mean renal inefficiency if the test is carried out during a period of persistent diuresis Under such conditions a dry diet cannot result in urine samples with a high specific gravity because of the large internal supply of water which is being mobilized and excreted at the time. As a matter of fact, even the dilution test may be normal when edema is not increasing or is absent temporarily Similar considerations apply to the chloride output in regard to renal function (51)

Given proper conditions for the various tests used (e g, intravenous, instead of intramuscular or subcutaneous, administration of phenolsulphonephthalein) normal renal function can be demonstrated in nephrosis throughout the ordinary clinical course, as it has actually been observed, although in advanced stages of nephrosis renal insufficiency should develop, hypothetically, when enough nephrons (glomeruli and their tubules) have been put out of commission This end stage has not yet been clearly described in uncomplicated nephrosis

but is undoubtedly a possibility The case reported by Shapiro (52) is very suggestive in this connection Yet the absence of renal insufficiency even after 17 years of active nephrosis in the patient recently studied by MacKay and Johnston (216) and Ehrich (215) arouses skepticism in regard to the so-called end stages of uncomplicated nephrosis Absence of increase in non-protein nitrogen of the blood is a characteristic feature of the autopsied cases of Fahr (15) (53) Lowenthal (10) (54), McElroy (17), Murphy and Warfield (29), Stepp and Petri (32) and others Clinically, increase in non-protein or urea nitrogen has been observed only during temporary periods of marked oliguria, or at a time of rapid mobilization of transudates into the blood stream with marked diuresis when the urinary output of nitrogenous material brought into the blood by the transudates might lag temporarily behind the excretion of water or salt

To quote all the authors who have observed *normal renal function* in nephrosis would be merely to repeat most of the preceding and succeeding references, since every case report involves some statement as to the adequacy of the kidneys However, in a series of papers by Van Slyke and his associates there is afforded the unusual opportunity of following a small but carefully and completely studied group of patients with nephrosis, in some instances for a period of several years In the protocols of these papers (100), (45), (153), (44), (83), (216) we find normal concentration tests, normal phenolsulphonephthalein outputs, normal blood non-protein nitrogen and urea nitrogen (except where urea was given in large doses as a diuretic), normal urea concentration indices (probably the most accurate practical test for renal function), normal urinary excretion of titratable acids and ammonia with normal ammonia acid ratios of one or more, indicating a normal ammonia production by the kidney, and a normal acid-base balance in the blood In short, in all of the above tests involving the behavior of the kidney as an organ for excretion of nitrogenous waste-products and foreign substances, or as an organ important in the maintenance of the acid-base balance in the blood and tissue-fluids, no essential impairment could be detected even in patients with repeated bouts of severe edema and albuminuria observed over long periods of time When one considers the gradual or sudden elimination of water and salt by such patients during each remission, at times with and at times

without the apparent aid of some therapeutic measure, it is difficult to believe that there existed any true renal impairment in regard to salt and water excretion Furthermore, the rapid onset or recurrence of edema with a vanishing chloride excretion and marked oliguria but without any other sign of renal insufficiency again leads one to feel that renal function in toto and in detail was probably normal throughout and that extra-renal factors were at work There is in fact less evidence of impaired renal function in the edema of nephrosis than in the definitely non-nephrotic edema of those cases of cardiac decompensation with kidneys normal except for decreased blood-flow. This normal renal function of nephrosis is such a striking paradox that it has led to novel and important theories of the pathogenesis of the disease and the syndromes that go under its name

1 Clinical course *Nephrosis* is par excellence a *chronic disease* and one subject to repeated changes for better or worse This variability refers particularly to the most conspicuous symptom, the edema During the periods of increasing or extensive transudation the patient is usually confined to bed for weeks or months and naturally experiences all of the disadvantages of such a regime, though it is a necessary one When edema has subsided sufficiently to enable the patient to get up and about, the underlying malnutrition in many instances remains a serious handicap In the more fortunate, or better treated cases, general health may be rapidly restored and the individuals even be able to undertake a moderate amount of work Persistent albuminuria, and a slight tendency to edema of the ankles in the evening, may be the only evidences of incomplete recovery Signs and symptoms of renal insufficiency, cardiac embarrassment or vascular accidents do not develop in the pure cases except in the very rare instances noted above Of course, where some underlying disease such as tuberculosis has resulted in the clinical picture of nephrosis, while anatomically there is amyloid plus lipoid renal degeneration, the course of the supposedly pure nephrosis becomes dependent upon the other condition and recovery is impossible Since these cases are not pure nephrosis, their course does not really affect the statements concerning the clinical outcome of uncomplicated nephrosis

It is during the relapses into an active transudative stage that the justly dreaded *complications* of nephrosis are most likely to occur

Some of these occur spontaneously, such as pneumococcus bronchitis, pneumonia, empyema or peritonitis, others are secondary to treatment, for instance, the streptococcus *cellulitis* or erysipelas, often fatal, which follows the surgical drainage of swollen limbs by incision, insertion of various cannulas, etc Even the strictest asepsis may not suffice to prevent infection in patients who have the low general resistance so evident in nephrosis *Pneumococcus peritonitis* is a common cause of death and at times seems to develop after repeated aspirations of ascitic fluid Whenever the ascitic fluid shows some increase in specific gravity or protein content, more cloudiness and higher cell count the possibility of pneumococcal or other form of bacterial peritonitis should be seriously borne in mind, particularly in children when a little abdominal tenderness, low-grade fever and slight leucocytosis are also present Slight rises in temperature are often overlooked in such cases or attributed to unknown factors Peritonitis in nephrosis may be a very insidious process without any of the stormy features seen in other types Repeated attacks of pneumococcus peritonitis may be survived, as pointed out by Davison and Salinger (55) and Schwarz and Kohn (56)

The *immediate causes of death* in patients with nephrosis are best determined from a review of the published autopsied cases Thus Fahr (15) (53) had nine cases in 5 of which peritonitis was the terminal event, in 1 pneumonia and peritonitis, in 2 empyema, and in 1 sepsis from drainage of the edematous tissues Lowenthal (10) (54) reported a total of 5 cases, in 1 of which a severe ulcerative colitis without peritonitis apparently led to death, in 1 erysipelas, in 1 parotitis followed by bronchopneumonia and cardiac failure, in 1 bronchitis, and in 1 peritonitis and bronchitis In McElroy's case (17) there were peritonitis, pleuritis and bronchopneumonia Murphy and Warfield (29) described a terminal attack of convulsions and coma in their case, during a period of severe edema, suggesting cerebral edema as the cause of death Volhard's (20) experience has been previously discussed and requires no further mention inasmuch as the cases overlap those of Fahr In the case report published by Stepp and Petri (32) the cause of death was not discovered at autopsy but there had been an erysipelas of the abdominal wall in the last month of the patient's life Schwarz and Kohn (56) found peritonitis at autopsy in 2 cases,

Lipoid degeneration (meaning by this term the deposition of doubly refracting lipoids) is always present in the affected tubules, in varying degree, but apparently bearing an inverse relationship to the extent of hyaline-droplet degeneration. Of course, ordinary isotropic fat is always associated with the anisotropic, even in the same cells or in the individual droplets. The distribution of the lipoid material is best seen in fresh, unstained sections when the typical Maltese crosses can be demonstrated. Characteristic staining reactions are described but in view of recent doubts cast upon these (63), (64), it seems better to adhere to the original criterion of *doubly refracting fluid crystals* in the polarizing microscope. Ordinarily the lipoids are seen in the cells lining the proximal convoluted tubules, in desquamated cells and leucocytes or in the detritus and casts in the lumen. In those kidneys in which considerable focal tubular atrophy has occurred the lipoids are set free in the interstitial connective tissue and remain there after complete disappearance of the tubular cells. In extreme instances most of the lipoid may be seen as masses between tubules, usually in large foamy cells considered by Lohlein (65) (66) to represent swollen lymphatic endothelial cords, but which may be enlarged fixed tissue phagocytes. It is these interstitial masses of lipoid material that produce the chalky streaked appearance of the "large white kidney." Lipoid deposition is found to be limited to the cortex, the medulla usually being quite free. In the ordinary sections prepared with the use of fat solvents, the lipoids are dissolved out and the cells take on a "washed-out," vacuolated or foamy appearance.

The *glomeruli* may be, and often are, entirely *normal*, using the term "normal" in its most rigid, histological sense and assuming a very careful examination, by an experienced and interested pathologist, of many glomeruli in sections taken from different parts of the kidney. They may show protein precipitate in the capsular spaces. Because of the repeated statements by Aschoff and other prominent German pathologists that the tubular degenerations described above were the sequel of an old, or burnt-out, glomerulonephritis, Fahr went over his material again, paying particular attention to the glomeruli. He found definite slight changes. These consisted of some widening and thickening of the capillary loops in some of the glomeruli, fatty or lipoid droplets in the glomerular endo- and epithelium with swelling

of the parietal cells of the capsule, in some instances adhesions between the tuft and capsule with minute calcium deposits at such points, or hyalinization and fusion of adjacent loops, rarely slight "rudimentary" proliferation of the epithelium near a hyalinized loop, but never the ordinary diffuse proliferative changes seen in glomerulonephritis of the Langhans type and so clearly delineated by Löhlein (67) Actual counts of the number of nuclei in the glomeruli indicated no increase beyond the normal, as would be the case in a true, even mild, inflammatory process The changes listed above were not found in the relatively early cases of nephrosis but seemed to increase with the duration of the disease, hence they were apparently secondary in origin Furthermore, they were distinctly focal in character, involving a relatively small number of the glomeruli Finally, definite crescent formation or other distinctive signs of glomerulitis were lacking in all cases and so astute an authority on glomerulonephritis as Lohlein was compelled to admit that in the sections submitted to him by Fahr there was nothing that resembled even remotely an old or recent glomerulonephritis (68) Fahr has applied the term "glomerulonephrosis" to these changes

The *arteries and arterioles* in the kidneys of patients with nephrosis have never shown any changes beyond those associated with the individual's age or a superimposed hypertension The latter is only a remote possibility since nephrosis is so predominantly a disease of the young

The *interstitial connective tissue* may show large deposits of lipoid material, as previously described In addition, in the more long standing cases, *focal scarring* appears in connection with casts that have stuck somewhere in the tubule, or consequent upon tubular atrophy Enough scarring may develop to give the appearance of early contraction, with concentric thickening and hyalinization of the glomerular capsules and atrophy of the tufts in those areas, just as occurs in the tubular contracted kidneys produced by hydronephrosis and chronic uranium poisoning At this stage considerable disorganization of renal architecture becomes apparent and areas of round cell infiltration are more numerous There is still, however, enough parenchyma left to have given a normal functional response in the living patient It is quite possible for one experienced in renal histo-

pathology to distinguish definitely even this advanced stage from chronic glomerulonephritis or other renal diseases

In addition to Fahr's cases, excellent descriptions of the pathological findings in typical nephrosis have been recently published in adequate detail by Lowenthal (10) (54) who reported 5 cases, by Murphy and Warfield (29), by McElroy (17), Cordier (213) Ehrich (215) and Shapiro (52) Lowenthal's and Shapiro's material are of special interest because a serious effort was made to find pathological changes in other organs besides the kidneys, particularly in the glands of internal secretion and in the reticulo-endothelial system The results of Lowenthal were entirely negative However, he observed in the first two of his cases, children aged four and one-half and eight years, *marked atheromatosis of the mitral valve and of the descending and abdominal aorta* in locations typical for senile atheromas Murphy and Warfield had the same experience in their patient aged twenty-one years and Murphy (69) has recently found a similar striking involvement of the ascending aorta in a boy of 12 with nephrotic glomerulonephritis. These lesions are of considerable importance in the problem of pathogenesis and will be discussed again under that heading

Case one, in the paper by Kaufman and Mason (70) was apparently one of pure nephrosis Less detailed descriptions of the microscopic findings in the kidneys of children with nephrosis, who were carefully studied clinically, are to be found in the papers of Davison and Salinger (55), Schwarz and Kohn (56) and DeLange (214) The limited autopsy report published by Major and Helwig (71) on a patient with apparently typical clinical nephrosis is difficult to interpret The glomeruli showed a "mild degree of acute glomerulitis" but no chronic changes, the lipoid in the kidney was not doubly refractile but gave staining reactions for phosphatides and the anatomical diagnosis was "chronic interstitial nephritis with lipoid infiltration "

Bell (72) on the basis of McGregor's (73) beautiful technic for the demonstration of the glomerular basement membrane and accurate differentiation between glomerular epithelium and endothelium, has described 4 cases of "pure lipoid nephrosis" in 3 of which, at autopsy, there were found thickening of the glomerular basement membrane and variable increase in the number of endothelial cells—in short, a picture differing only in degree from that obtained in intracapillary

glomerulonephritis It will be shown later, in the sections on theories of pathogenesis and differential diagnosis, that these important morphological findings occurred in cases, which, even clinically, were probably not "pure lipoid nephrosis," but the usual nephrotic glomerulonephritis However, further studies with this technic on more typical material will probably yield valuable information and may help to settle the difficult problem of the early glomerular changes in nephrosis

c *Nephrotic contracted kidney* Definitely contracted kidneys resulting from nephrosis uncomplicated by amyloidosis are extremely rare if one demands that clinical nephrosis had existed during life Munk (74), on purely anatomical grounds, selected 6 cases of supposedly luetic nephrotic contracted kidneys from among a large series of routine autopsy cases These kidneys were characterized by multiple, irregular, fine granulation of the surface with narrowing of the cortex and obliteration of the usual markings There were found, microscopically, focal anisotropic lipoid degeneration and complete atrophy of the tubules The glomeruli, on the other hand, were well preserved but showed a striking lipoid degeneration of the visceral or parietal epithelium or of the entire tuft and capsule Unfortunately, most of the patients were over thirty years old and arteriosclerotic changes complicated the picture Furthermore, the clinical data obtainable were very meager, in only 2 or 3 was there a history of edema at some time or other In none of the 6 patients was renal disease the cause of death and in none did there exist any definite symptoms of renal disease upon admission to the hospital Munk considered the above changes identical with Orth's "nephritis interstitialis chronica fibrosa multiplex syphilitica" and as representing a form of nephrotic contracted kidney In the absence of accurate clinical records it is impossible to draw any definite conclusions from pathological findings alone, particularly in older individuals in whom arteriosclerosis, hydronephrosis, amyloidosis, or other renal lesions may lead to similar pictures Clinical and pathological points of view must be interdependent

In contrast to these cases of Munk is the case of known clinical nephrosis reported by Ehrich (215), in which the *patient had had recurrent edema for about 17 years* Death occurred from hemolytic streptococcus peritonitis at the age of 19 At autopsy, *the kidneys*

were markedly enlarged, each weighing about 300 grams In addition to the typical pathological picture of nephrosis there were considerable focal scarring and varying degrees of hyalinization of about half of the glomeruli, chiefly in the fibrotic regions About a third of the glomeruli were entirely hyalinized The careful study of these kidneys by Ehrich failed to reveal any evidence of glomerulonephritis The author concluded that "it seems to be doubtful whether true lipoid nephrosis leads to contracted kidneys"

Recently, in a critical review of nephrosis, Shapiro (52) reported, among others, an autopsy on a luetic patient, aged twenty-six, who while under active antiluetic therapy developed a typical clinical nephrosis, with six recurrent periods of edema and with a normal blood pressure throughout, but with progressive impairment of renal function, normal at first, to the stage of definite renal insufficiency with increasing anemia, and death within 7 months from the onset of edema The heart weighed 220 grams The kidneys together weighed only 164 grams, showed a smooth surface and, microscopically, presented marked interstitial fibrosis with atrophic tubules and heavy anisotropic lipoid deposits The other tubules were dilated but presented no active degeneration or regeneration The glomeruli were small but otherwise normal, except that some showed fusion and narrowing of some of the capillary loops, with occasional hyalinization of individual loops The author considered this case as one of pure nephrotic contraction since no inflammatory nor arterial changes were present to account for the extreme atrophy of tubules and the interstitial fibrosis It is difficult to understand how such marked changes could occur in 7 months unless the preceding heavy metal treatment played a rôle It would be very important to have more cases reported, as this one was, with careful clinical and pathological studies

Thannhauser and Krauss (75) reported a case of nephrotic contracted kidney that deserves some discussion at this point because it illustrates the difficulties that may confront even experienced clinicians in their interpretations of clinical and pathological data The patient, who suffered from multiple myeloma, with heavy Bence-Jones proteinuria and slight serum-albuminuria, developed some edema of the face, ankles and parietes in the last four and one-half months of his life This edema persisted in spite of polyuria and loss of weight and was

unassociated with increase in blood pressure but was accompanied by a gradual rise in the blood non-protein nitrogen to a very high terminal figure, 212 mgm A severe anemia developed, along with a gradual fall in the serum proteins Death occurred from pneumonia The kidneys were considerably reduced in size, but *perfectly smooth* "small, white kidneys" Microscopically, the glomeruli were entirely normal No amyloid was present There were many atrophic areas in which the tubules were completely disintegrated and replaced by fibrous tissue In these areas were "protein stones" (lamellated, uncalcified, protein masses, presumably the Bence-Jones and other precipitated proteins) surrounded by foreign body reactive zones While considerable fat was demonstrated in the tubules by Sudan III staining, no mention is made of doubly refracting lipoids The shrinkage of the kidneys was obviously due to the marked tubular atrophy Was this a true nephrosis and, therefore, a true nephrotic contracted kidney?

The rapid course of four and one-half months, the presence of only moderate edema, and the very possible rôle of emaciation in accounting for the edema, the polyuria and the decreased serum proteins, seem to point against a true clinical nephrosis On the other hand, the autopsy findings in the kidneys could just as well, if not better, be explained on the basis of prolonged tubular damage and destruction by the large amount of Bence-Jones protein excreted In favor of this view was the presence of the "protein stones" in the scarred areas In other words, on the evidence presented in their paper, Thannhauser and Krauss were probably not justified in assuming that they were dealing with a contracted lipoid nephrotic kidney Yet, they have been frequently so credited by various authors

Very recently, Perla and Hutner (217) have published an excellent report on two cases of multiple myeloma in which the kidneys were small, smooth and white Microscopic examination showed extensive destruction of tubules in both cortex and medulla, replacement fibrosis, interstitial lymphocytic infiltration, many casts in the intact but dilated convoluted tubules, and practically normal glomeruli These authors, however, clearly distinguish the above "severe nephrosis" from lipoid, or genuine, nephrosis This distinction seems fully justified in the interests of such a clear cut clinical and pathological syn-

drome as nephrosis The absence of the clinical nephrotic syndrome in the cases of Perla and Hutner tends to throw further doubt on the existence of a true nephrosis in the patient studied by Thannhauser and Krauss

d Specificity of anisotropic lipoid degeneration As stated in the introduction to this review, the term "nephrosis" had its origin in the morphological concept of non-inflammatory, degenerative tubular lesions in the kidney Since there were many forms of degeneration possible—albuminous, hyaline-droplet, hydropic, fatty, etc —"nephrosis" became a broad term to pathologists, including a variety of renal lesions many of which had no distinctive clinical correlatives It was Munk's great contribution to single out "lipoid degeneration" characterized by the presence of the *doubly refracting lipoids* (cholesterol esters) originally described in normal and diseased human organs by Kaiserling and Orgler (35) In 1908, Munk (76) clearly reviewed the entire subject of degenerations and pointed out that "lipoid degeneration" occurred only in the living body and during a gradual death of the cells He considered this process as irreversible, in contrast to the ordinary fatty degeneration and infiltration By 1913, Munk (3) had definitely established the relationship between doubly refracting lipoid droplets in the urine and "lipoid degeneration" in the kidney He was the first to emphasize the importance of the latter in primary degenerative renal disease (nephrosis), although Lohlein (65) (66) (67) had very early described in complete detail the "lipoid degeneration" occurring in glomerulonephritis and amyloid disease of the kidneys, with especial reference to the massive interstitial deposits of doubly refracting lipoids found in the "large, white kidneys" and the rather focal distribution of the lipoids in contrast to the diffuse process in ordinary fatty infiltration

The pathologist can scarcely make a diagnosis of nephrosis unless doubly refracting lipoid (cholesterol esters) is found in the tubular epithelium, in the interstitial connective tissue or in both The mere presence of such lipoids, however, by no means makes nephrosis a likelihood since a vast number of kidneys containing them show various stages of glomerulonephritis This was pointed out by Kaiserling and Orlger (35), Lohlein (65 (66) (67) (68), Munk (4), M'Nee (62) and recently in an excellent review by Murphy (77) Those cases which at

autopsy show considerable lipoid degeneration with a mild intracapillary glomerulonephritis are just the ones which the clinician has the greatest difficulty in differentiating from pure nephrosis, for there may be little or no clinical evidence of renal inflammation while the nephrotic syndrome is predominant Likewise, lipoid degeneration is quite common in kidneys showing amyloidosis and is in these instances also associated with a clinical picture resembling that of nephrosis

Munk (26) has pointed out that none of the poisons which produce ordinary fatty degeneration of the kidneys give rise to anisotropic lipoid degeneration, nor does the virus of any disease do so except that of lues, which gives a typical nephrosis The metabolic disturbances, including the severe anemias, often are associated with extreme fatty degeneration yet never with lipoid degeneration This holds even for severe diabetic lipemia Lubarsch (78) in his enormous experience with degenerations and pigmentations does not refer to doubly refracting lipoids except in the "nephrotic types" of renal disease Fahr (61) has never seen doubly refracting lipoids in those kidneys showing extreme fatty changes due to phosphorous poisoning Iwantscheff (79) has recently made a study of the lipoid deposits in the liver and kidneys in various conditions, using histochemical and polarization methods Cholesterol esters (doubly refractile lipoids) were found in the kidney only in glomerulonephritis, in amyloidosis and in contracted kidneys (there was no case of uncomplicated nephrosis in this series) They were not found in tuberculosis, in diabetes mellitus, in senility, or in cirrhosis of the liver, in all of which neutral fats and kephalin were predominant In the liver, lipoid material usually consisted of neutral fat with a shell of doubly refractile lipoid, although the Kupffer cells might contain considerable doubly refractile lipoid in diabetes and hepatic cirrhosis The most interesting feature, however, was the absence of such lipoids in the Kupffer cells of the liver in cases of glomerulonephritis with much doubly refracting lipoid in the kidneys Jaffe (80) has observed a small amount of anisotropic lipoid infiltration in the kidneys of a patient who died of mushroom poisoning Fex (81) found doubly refracting fluid crystals in the kidneys only in chronic renal disease and not in diabetic coma, pernicious anemia or cirrhosis of the liver In short, while ordinary fatty deposits may be found in conjunction with a host of conditions, doubly refracting lipoids occur

mainly in those diseases of the kidney—nephrosis, amyloidosis and glomerulonephritis—characterized clinically by the nephrotic syndrome To this extent anisotropic lipoid degeneration in the kidneys is a specific pathological finding, vastly narrower in its clinical associations than the other degenerations or infiltrations and therefore of greater, because of more definite, significance Exceptions to this conclusion seem to be cases of carcinoma referred to by Munk (82) in which the kidneys may show lipoid degeneration of the tubules without the clinical counterparts existing. Confirmation of this observation is needed The question of the specificity of the lipoid degeneration in nephrosis has an important bearing upon the pathogenesis of the disease and will be discussed again It may be stated here that Fahr (61) considers lipoid degeneration as occurring at the very beginning of the disease

PATHOGENESIS OF NEPHROSIS

Several attempts have been made to explain the pathogenesis of nephrosis on the basis of some uniform concept This has involved the assumption of a primary renal disease, a primary general or metabolic disturbance, or some combination of the two Before discussing these synthetic points of view it will be necessary to analyze in detail the changes in the urine, blood, and tissue-fluids, which must be individually explained by any comprehensive theory of pathogenesis of the disease as a whole Loop-holes in our knowledge concerning the various aspects of nephrosis will thereby become more evident Stumbling blocks to the various theories will also emerge

A Albuminuria

The marked proteinuria in the active stages of nephrosis has already been referred to and is the most significant urinary feature of the disease The earlier work on the nature of the urinary proteins, while fairly extensive, is difficult to evaluate in relation to nephrosis because there is no way of deciding upon the diagnosis of the cases involved This drawback, however, is of no special import in regard to the theoretical considerations of the effect of prolonged and heavy albuminuria, whatever the disease in which such occurs Most of the case reports on nephrosis give no quantitative data on urinary proteins other than

the familiar Esbach concentration figures Recently, however, a careful study over a period of years has been reported by Hiller, McIntosh and Van Slyke (83) who also reviewed the previous work on the subject In 5 cases of uncomplicated nephrosis, the daily output of urinary proteins varied between 4 2 and 20 grams, with considerable fluctuation in the individual case It is extremely significant that *from 85 to 95 per cent of the urinary protein was albumin* and only 5 to 15 per cent globulin, giving a urinary $\frac{\text{albumin}}{\text{globulin}}$ ratio of from 5 to 22 In fact the ratio was greater than 10 in 4 cases out of the 5 These figures are based upon the averages of repeated determinations on different days, since single analyses mean little where there is so much variability in the total output and in the two main protein fractions Errors in technique were ruled out Using a different method, Schlutz, Swanson and Ziegler (84) reported urinary $\frac{\text{albumin}}{\text{globulin}}$ ratios varying enormously in 4 cases of nephrosis, in children With total protein outputs of 8 to 22 grams daily, the ratios usually were 2 or less while ratios of 40, 60 and even 80 were obtained when the output was lower When very small amounts of protein are excreted it is difficult to draw accurate conclusions The high proportion of albumin in the proteinuria of nephrosis is particularly striking when compared to the $\frac{\text{albumin}}{\text{globulin}}$ ratios in chronic nephritis with definite renal function impairment In 15 out of 19 such cases reported by Hiller, McIntosh, and Van Slyke (83) the ratios fall between 2 and 5, in the other 4, between 5 and 10 The globulin excretion, therefore, was much more pronounced in inflammatory renal disease than in nephrosis

Geill (218) investigated the urinary excretion of protein in 11 cases of renal disease, none of which was an instance of pure nephrosis In nephrotic glomerulonephritis the urinary $\frac{\text{albumin}}{\text{globulin}}$ ratios fell between 9 and 19, in acute nephritis around 5, in chronic glomerulonephritis between 2 and 4, in amyloid disease 1 or less shortly before death The globulin excretion was, therefore, most marked in amyloid disease of the kidneys In one patient with this disease, Geill calculated that half of the total serum albumin and globulin was lost daily in the urine

There has been much speculation but almost no published work on the difficult problem of the true nature of the urinary proteins in nephrosis While no one has seriously disputed their origin from the plasma it is impossible to state from present knowledge whether the urinary albumin and globulin as they leave the plasma represent perfectly normal proteins or proteins changed and hence more readily excreted Erben (85) was able to demonstrate by precipitin tests that part, at least, of the urinary albumin and globulin in cases of "chronic parenchymatous nephritis" was identical with the corresponding serum fractions F Muller (9) in his second great review of renal diseases stated that precipitin reactions failed to demonstrate in cases of nephrosis any protein in the urine different from those in the serum However, since this remark was made, considerable improvement has taken place in the methods available for identifying proteins and this interesting subject should be investigated thoroughly in view of the importance of either negative or positive findings Recently Hewitt (86) has studied the optical rotatory powers of highly purified, undenatured serum and urine albumins obtained from four cases of chronic "nephritic" edema, with and without uremia, and two cases with albuminuria of pregnancy In all of these, virtually identical optical rotations were found for the albumins of the sera and the urines This fact led the author to conclude that serum albumin passed through the kidney unchanged Further evidence was published by Hewitt in 1929 (87) when he demonstrated that the mean value for the specific rotatory powers of the urinary albumin in nephrosis, the albuminuria of pregnancy and eclampsia was identical with the corresponding figure for normal serum albumin The refractive indices of the purified serum and urine albumins were indistinguishable, nor could any differentiation be made by means of the ultra-violet absorption spectra These results of Hewitt stand in sharp contrast to the claims of Thomas, Schlegel and Andrews (88), Andrews and Thomas (89) and Andrews, Thomas and Welker (90), who believe they have evidence to show that "nephritis is not a renal disease but a disturbance in mineral metabolism causing disintegration of the great parenchymatous organs," as a result of which tissue proteins and toxic protein split-products enter the circulation and are excreted, by the kidney, either directly or in combination with the serum proteins From this point

of view albuminuria becomes a highly protective mechanism in the detoxication of poisonous tissue proteoses While these investigators do not refer specifically to nephrotic albuminuria, it is obvious that a similar line of reasoning must apply to this most extreme form of albuminuria Much more evidence is necessary than the authors present in support of their hypothesis of proteinuria Cavett (219) has attacked the problem from a purely chemical standpoint He analyzed the proteins in urine, plasma and edema fluid by the Van Slyke fractionation process Excellent conformity was obtained between the values for normal plasma proteins and those in material from edematous patients The racemization (sodium hydroxide) curves for the individual proteins showed a similar identity of the plasma, urinary, and transudate proteins with the normal plasma proteins The whole pathogenesis of the disease under discussion really rests upon this one question—are the urinary and plasma proteins qualitatively or biologically different from the normal? The subsidiary problem of the glomerular versus tubular excretion of the protein is largely a matter of view-point, insusceptible at present of direct proof

B Low serum or plasma proteins

In 1827 Richard Bright (7) incorporated in his reports some remarks by Bostock on low serum proteins found in patients with heavy proteinuria, and shrewdly drew the conclusion that the former was secondary to the latter In 1831 Bright (7) published Babington's figure of 5 per cent "albumen" in the serum (specific gravity 1 021) of a young woman with albuminuria and anasarca of 3 years duration The urinary "albumen" was 1 per cent The normal serum "albumen" was stated to be 8 to 10 per cent These figures while not very accurate have a striking resemblance to recent reports

No attempt will be made to review in its entirety the literature on low serum proteins in patients with albuminuria and edema The findings are monotonously uniform and appear in almost every case report In a case of nephrosis following upon syphilis in a man of 22, Javal (22) was perhaps the first investigator to publish a series of serum protein analyses and to comment upon their significance His patient excreted 25 to 30 grams of protein daily for almost a year and was

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markedly edematous during that period. The serum proteins were 5.2, 6.6 and 7.2 grams per cent (refractometrically), the last figure occurring when the patient no longer had edema nor ascites, and albuminuria of only 2 grams daily. The classical work on serum proteins, however, was done by Epstein, who in 1912 (91) published his observations upon "chronic parenchymatous nephritis." Using chemical methods of analysis, he found total protein figures from 2.731 to 5.125 grams per cent in 2 patients with "parenchymatous nephritis" and noted the low or reversed $\frac{\text{albumin}}{\text{globulin}}$ ratios, 0.133 to 0.80, a fact already emphasized in 1905 by Erben (92). From 1917 on, in a series of publications (5) (93) (94) (27) (95) (11) Epstein laid the greatest emphasis upon the low serum proteins in active nephrosis and was largely responsible for the impetus which resulted in an enormous amount of careful and valuable work upon this aspect and related phases of nephrosis. His observations were widely confirmed although variations in the actual figures were introduced by the use of different methods. Rowe (96) found in "chronic nephritis with edema" total serum proteins of 3.8 to 4.6 grams per cent and $\frac{\text{albumin}}{\text{globulin}}$ ratios of 1 to 1.9, the proteins, especially the albumin, rising as the edema disappeared. He stated "Chronic nephritis with edema shows the lowest values for total serum proteins obtained in disease." Low serum proteins, with serum albumin down to 1.27 grams per cent were found in nephrosis by Fodor and Fischer (97). Kollert, in 1923 (98) reported similar changes, with particular emphasis upon the increased plasma fibrinogen. This normally forms only about 3 to 5 per cent of the total plasma protein and comes down with the globulin fraction. Kollert reported 4 to 9 times the normal amount of fibrinogen in the plasma of nephrotic patients. Schwarz and Kohn (99) found serum proteins between 4 and 6 grams per cent in a series of children with edema and albuminuria. Perhaps the most complete study on the plasma proteins in patients with renal disease, who were followed for long periods, was published by Linder, Lundsgaard and Van Slyke (100), using reliable chemical methods. The plasma proteins of edematous patients ranged from 3.5 to 5.5 grams per cent while in 2 cases of typical nephrosis they fell between 3.60 and 5.08 grams per cent, with

$\frac{\text{albumin}}{\text{globulin}}$ ratios usually 0.40 to 0.60 (normally 1.4 to 2.0). A very important contribution by these authors was the unequivocal demonstration of *normal plasma volumes* in these two patients during various stages of edema or diuresis. *This dealt the final blow to the old theory of "hydremic plethora"* and proved that the plasma proteins were absolutely diminished in amount as well as in concentration per given volume. Fahr and Swanson (101) found the total serum proteins below 5 grams per cent in 7 analyses out of 9 on 3 cases of nephrosis. The serum albumin was below 2 grams per cent in 4, between 2 and 3 grams per cent in 5 analyses. Further studies on the low plasma proteins in active nephrosis with emphasis on plasma albumin values below 2 grams per cent were reported incidentally by Leiter (102). Hiller, McIntosh, and Van Slyke added more data, essentially consistent with the above, in 1927 (83). Krogh (103), Schade and Claussen (104), Govaerts (105), Rusznyák (106), Kollert and Hartl (107), Clausen (108), Cope (109), Mayrs (110), Blackfan and Hamilton (41), to mention only the publications with fairly extensive data, have all found low total proteins in active nephrosis or the nephrotic syndrome, with usually a marked decrease in the $\frac{\text{albumin}}{\text{globulin}}$ ratios. The latter, however, are quite variable and when the total proteins are only moderately diminished need not be strikingly abnormal. There is nothing specific about a reversed $\frac{\text{albumin}}{\text{globulin}}$ ratio, i.e. a ratio of less than one, for nephrosis or the nephrotic syndrome. Whenever the total plasma proteins are considerably reduced in disease, by albuminuria, exudation into serous cavities, protein starvation and general undernutrition, or experimentally by direct removal of plasma, the ratio may fall below the normal or even become reversed due to a predominant loss of albumin, to a much more rapid regeneration of the globulin than the albumin fraction or to both of these factors. The same phenomenon may occur during infections and immunity processes when, with the plasma albumin decreased or unchanged, a rise occurs in the globulin fraction, reflecting itself in a decreased ratio. The absolute values for plasma albumin and globulin are far more important than the $\frac{\text{albumin}}{\text{globulin}}$ ratio, to which a great deal of significance has

hitherto been attached It must also be added, that chemical methods of analysis are to be decidedly preferred to refractometric, nephelometric and other physical methods in view of the increased lipoids in the plasma in nephrosis and the probable alterations in the physical state of all the colloids in the blood

The idea consistently sponsored by Epstein (5) (11) that there is a direct relationship between the albuminuria in nephrosis and the reduction in the plasma proteins has now obtained fairly general acceptance in its main thesis, if not in individual details Thus, Linder, Lundsgaard and Van Slyke (100) found low plasma protein figures when the urinary output of protein reached one gram daily or more When albuminuria decreased to a trace in one of their patients with nephrosis the plasma proteins rose to almost 7 grams per cent In cases of nephrotic glomerulonephritis in which albuminuria of 4 to 12 grams daily persisted the plasma proteins remained between 4 and 6 grams per cent even months after edema had subsided In the case reported by Javal (22), mentioned previously, the serum proteins returned toward the normal level only after the albuminuria had decreased from 25 grams daily to 2 grams While many authors refer to such a relationship between urinary and plasma proteins, only a few detailed studies of recent data are available Hiller, McIntosh and Van Slyke (83) made this problem the basis for specific study and published a very complete report In this it was shown that there was a definite, though rather rough, relationship between the plasma protein level and the 24 hour urinary output averaged over long periods of time Thus, where the average daily proteinuria was 5 3, 5 8, 8 6 and 9 8 grams respectively the plasma proteins ranged between 6 and 7, 5 and 6, 4 and 5, 3 and 4 grams per cent, respectively Furthermore, in nephrosis high urinary $\frac{\text{albumin}}{\text{globulin}}$ ratios were found with low plasma ratios, the urinary ratios were lower and the plasma ratios higher in chronic nephritis Schlutz, Swanson and Ziegler (84) also pointed out that a high urinary protein excretion was associated with low plasma proteins, and low urinary protein outputs with more nearly normal plasma protein figures Kollert and Hartl (107) reached the same conclusions, so did Geill (218)

The inverse relationship between urinary and plasma proteins is very

far from being an exact one However, when it is remembered that excretion in the urine is not the only factor and that loss of protein into massive transudates and particularly decreased formation of plasma proteins due to intrinsic, or extrinsic dietary, influences must play a large rôle in the actual level of the plasma proteins at any given moment, then it is really remarkable that even a rough correlation can be found To expect a strictly quantitative fall of the plasma proteins with increasing urinary protein excretion is to ignore the other important variables The mass of evidence points, however, to a cause and effect relationship between the two

C Edema

a Albuminuria, low plasma proteins and edema The peculiar edema of nephrosis has been of unusual interest to many because it seems to represent a beautiful example of an extra-renal (non-renal), non-cardiac, form of general edema, occurring in what is, at firstglance, a serious type of renal disease and forming the most important symptom of this disease This sounds paradoxical, yet no one at present seriously believes that the edema of nephrosis is of renal origin in the sense of retention of salt and water due to renal insufficiency The hydremia of nephrosis, as pointed out before, is due not to hydremic plethora or increased plasma volume but simply to decreased protein content, as even Bright suspected The oliguria is due, largely, to extra-renal deviation of available water, as pointed out by Volhard (20) and many others Since renal function is normal in every respect in nephrosis and since measures that do not act on the kidneys specifically may suddenly lead to marked diuresis, there apparently remains nothing at all to indicate that the edema of nephrosis is related to the kidneys Actually, however, one connecting link is left between the kidneys and nephrotic edema—albuminuria, marked and persistent over long periods of time

It was Epstein (5) who first indicated in no uncertain terms the unique value of Starling's views on fluid exchange in the body in explaining the obstinate edema of nephrosis He stated clearly that as a result of albuminuria the plasma proteins were reduced to such a level that the *colloid osmotic pressure of the plasma* was no longer sufficient to counterbalance the hydrostatic pressure in the capillaries,

which constantly tends to force fluid out of the blood and into the tissue-spaces Hence, more fluid was pushed into the tissues than dragged back again by the osmotic effect of the non-diffusible plasma proteins, and edema was inevitable Edema, in nephrosis, was thus merely an unusual variation on one side of what is normally a physiologically balanced system This ingenious and original application of a classical physiological theory to an important problem in pathological physiology remained only a theory until actual measurements were made of the osmotic pressure of the plasma or serum proteins in clinical cases of nephrosis The first of these is recorded by Krogh (103), as of 1922 In a patient with nephrotic edema Hagedorn, Rasmussen and Rehberg found the capillary blood pressure to be 150 mm of water, while the colloid osmotic pressure was only 100 mm of water (normally 450 mm) due to low plasma proteins—5 grams per cent Here, therefore, there was a head of pressure of 50 mm of water in favor of filtration of fluids from the blood into the tissue-spaces, enough to explain much of the edema present, other factors being equal It is very interesting that in this same patient, the urine contained 2 8 grams per cent of protein, giving a colloid osmotic pressure of 240 mm of water In other words, osmotically active protein molecules (presumably albumin chiefly) were present in greater concentration in the urine than in the blood

This classical observation has been amply confirmed by later work. In a large series of cases Govaerts (105) (111), applying direct osmometry to the serum, found the normal osmotic pressure of the proteins to lie between 35 and 40 cm of water or about 4 6 cm of water per gram of protein per cent ("unit" protein osmotic pressure) In nephrotic edema the osmotic pressure fell to 12 to 15 cm with the usual marked reduction in plasma proteins In other edemas, such as cardiac and cachectic forms, pressures ranging between 15 and 30 cm of water were found, varying apparently with the changes in the serum protein level At about the same time, but with quite a different method, Schade and Claussen (104) determined the normal "oncotic" (osmotic) pressure of the plasma colloids and found that it varied between 31 and 37 cm of water In nephrotic edema there was regularly a low value, 15 to 27 cm of water, with parallelism between the extent of edema and the degree of lowering of the osmotic

pressure In non-edematous forms of renal disease the "oncotic" pressure was normal Rusznyák (106), using a method not comparable to the above, found the total osmotic pressure of the plasma colloids in non edematous patients to vary from 16 5 to 27 9 cm of water and the pressure per gram of protein per cent from 2 5 to 3 5 cm of water However, in 2 patients with a nephrotic syndrome the total osmotic pressure ranged between 4 6 and 5 7 cm of water and the pressure per gram of protein per cent between 0 9 and 1 1 cm The method used accounts for the wide divergence of the absolute values from those of other authors However, the relative differences are significant In an extensive review of the entire subject, Mayrs (110) pointed out the inadequacy of the objections to the Starling-Epstein theory of nephrotic edema and described another method for the determination of the osmotic pressure of the plasma proteins In 5 cases of "hydremic nephritis" the plasma proteins varied from 4 46 to 5 32 grams per cent, the total osmotic pressure from 8 9 to 14 3 cm of water, the "unit" osmotic pressure (pressure per gram of protein per cent) from 1 97 to 2 69 cm of water Cases of acute nephritis showed total pressure values of 10 to 30 cm of water, the higher ones occurring with decrease in edema, and concomitant variations in plasma proteins, 4 67 to 7 19 grams per cent Normal osmotic pressure values were about 40 cm of water with "unit" pressures of about 5 cm of water Nephrotic edema was never seen when the osmotic pressure was higher than 20 cm of water Iversen and Nakazawa (112) (113), using Krogh's osmometer, found the osmotic pressure of the serum to vary from 32 5 to 40 1 cm of water with 4 74 cm of water pressure per gram of protein per cent In 3 cases with a nephrotic type of edema the total osmotic pressure values were 8 9, 9 0 and 12 5 cm of water with unit pressure values of 1 3, 2 0 and 2 6 cm The "unit" pressure values for the urines of these patients were, respectively, 11 2, 7 6 [illegible] cm of water In other words, the urine contained in a given [illegible] more of the osmotically-active protein molecules (the smaller [illegible] molecules) than did the serum, pointing very definitely to [illegible] as the cause of the other changes The critical zone [illegible] pressure of the serum, below which edema was present [illegible] it was absent, ranged between 24 0 and 27 0 cm of [illegible] thorough investigation in this field was reported by [illegible]

used a modification of Govaerts' method, with chemical determinations of the serum proteins. His figures for osmotic pressure of the serum proteins were 30 to 32 cm of water in normal individuals, 27 to 48 cm in 11 cases of nephritis without edema, 8 to 28 cm in 10 cases of nephritis with edema The last group includes both acute and chronic forms In the nephrotic types, with marked edema, the osmotic pressure of the serum was uniformly low, about 15 cm of water, and in one case of "pure nephrosis" it lay between 8 0 and 11 3 cm with a pressure per gram of protein per cent of only 1 92 to 2 42 cm of water, compared with 4 32 to 6 80 cm, essentially normal values, in the non-edematous nephritic group

The above figures have been quoted in detail to illustrate that, in spite of the widely different methods used, the considerable variation in the absolute values and probable inperfections in the techniques employed, there is uniform agreement on two facts (*a*) that the total osmotic pressure of the serum proteins is markedly reduced in nephrotic edema, as one would expect from the low concentration of proteins in the serum, (*b*) that the fall in osmotic pressure is out of proportion to the reduction in the total serum proteins This latter fact was a puzzle originally to Schade and Claussen (104) who experienced difficulty in attempting to correlate the osmotic pressure with the percentage of serum proteins Unfortunately, they used refractometric instead of chemical analysis and took no account of the $\frac{\text{albumin}}{\text{globulin}}$ ratio As a result they missed a beautiful relationship later worked out by Govaerts (111) who clearly saw, and virtually proved, that the smaller serum albumin molecules had a higher osmotic pressure per gram of protein than the much larger serum globulin molecules. Since in nephrotic sera the albumin fraction is often relatively much lower than the globulin, giving a low or reversed $\frac{\text{albumin}}{\text{globulin}}$ ratio, it becomes apparent that one serum with 5 per cent of protein may yield a much lower osmotic pressure, both absolutely and per gram of protein, than another serum with the same total protein content if the first has less albumin and more globulin than the second Govaerts calculated from chemical and osmometric comparisons of sera with varying protein contents and different $\frac{\text{albumin}}{\text{globulin}}$ ratios, that one gram

of albumin per cent gave an osmotic pressure of about 7 50 cm of water while 1 gram of globulin per cent gave a pressure of only 1 95 cm He was able to predict the osmometric readings fairly accurately from the chemical analyses on using the above values When he plotted osmotic pressure figures against $\frac{\text{albumin}}{\text{globulin}}$ ratios a *fairly smooth curve resulted* These findings of Govaerts have not been disproved, and they are of great importance in helping to explain some of the inconsistencies noted by various authors in the relationship between low plasma proteins and edema On the other hand, his and other figures should be accepted with some reserve as was pointed out by Krogh (114) and Hastings (115), in view of the difficulties involved in the actual measurements and the arbitrary nature of the division of the serum proteins into two groups only

In regard to *the origin of the measurable osmotic pressure of the plasma or serum proteins*, Rusznyák (106) attributed the phenomenon to the effect of the Donnan equilibrium He emphasized the fact that at the ordinary pH of the plasma the albumin fraction was farther removed from its isoelectric point than the globulin fraction, and hence, had a higher osmotic effect per gram of protein However, this point of view is difficult to reconcile with the experimental and theoretical considerations contributed to this problem by other investigators Thus, Hastings (116) has calculated, on the basis of accurate studies upon the distribution of electrolytes between the serum and the transudates in nephrotic edema (117), that the differential osmotic pressure in favor of the serum, due to the Donnan equilibrium effect, was only about 4 mm Hg, or 5 4 cm of water On the other hand, the sum of the osmotic pressures of isoelectric albumin and globulin, calculated from their known molecular weights and concentration in normal serum, roughly approximated the value of 22 mm Hg, more than five times the pressure due to the Donnan effect Confirmatory evidence may be found in the paper of Marrack and Hewitt (118) They calculated, on theoretical grounds, that under normal conditions a change in pH from 7 0 to 8 0 should give rise to an increase in osmotic pressure of 6 5 cm of water, or 4 8 mm Hg, on the basis of the Donnan effect Actual measurements showed even less variation than this, usually not more than 1 cm of water for a change in pH from 6 8 to 8 0

Mayrs (110) found practically no measurable variation in the osmotic pressure of the serum proteins even with marked differences in pH In view of all this, Rusznyák's contention must be set aside and the greater part of the protein osmotic pressure attributed to the unionized protein molecules

Linder, Lundsgaard and Van Slyke (100) stated that the greatest decrease in plasma proteins did not correspond to the greatest extent of edema while, on the other hand, a considerable decrease in plasma proteins was compatible with absence of edema This statement has been widely quoted, and apparently confirmed by such authors as Fahr and Swanson (101), Schwarz and Kohn (99), and Mason (119). If one, however, takes into consideration not only the total plasma proteins, but the osmotically more active albumin fraction, then fair correlation may be shown to exist in the above references between the presence and obstinacy of edema and low plasma albumins (below 2 grams per cent) provided the total proteins are not above 5 per cent, in other words, the globulin must not be sufficiently elevated to increase the total osmotic pressure to above 20 cm of water The total plasma proteins may increase considerably, due to a rise in the labile globulin fraction only, with so slight an effect on the total osmotic pressure as to be insignificant in relation to edema Yet an increase of only 0 5 gram per cent in the albumin fraction may be sufficient, even with unchanged total plasma proteins, to raise the osmotic pressure above the critical level for the persistence of edema Moore and Van Slyke (220) have observed an almost perfect correlation between the reduced plasma protein content and the presence of edema in 75 successive patients Krogh (114) has pointed out that since the normal plasma protein osmotic pressure is nearly three times the average capillary blood-pressure (filtration pressure), a very considerable fall in the former may be consistently compatible with absence of edema This fact has not been considered by most authors but is emphasized by Mayrs (110) It is also unfair to deny a relationship between low plasma proteins and edema merely because the proteins did not increase as the patient lost edema following paracentesis of the abdomen or chest, the use of powerful diuretics and other measures whose effects vary in location Decrease of edema in such cases simply goes to show what every one is willing to grant—that there are other factors

besides the osmotic pressure of the plasma proteins in the regulation of the water-balance in the body This does not weaken, however, the important rôle of the plasma proteins in the *untreated organism* On the other hand, due consideration must also be given to the general concept of physiological regulation of the volume of the body in contradistinction to local mechanisms, as was clearly expressed by McLean (120)

Only a few instances are available in the literature in which the osmotic pressure of the serum proteins has been followed during changes in, or disappearance of, edema Such have been noted by Mayrs (110) and already referred to above With decrease in edema the osmotic pressure of the serum proteins rose Cope (109) has observed that significant increases in the osmotic pressure may occur in convalescent cases of acute nephritis some time before the total protein concentration rises This might account for some of the discrepancies in the literature As the edema disappears in acute nephritis there is always, according to Cope, a return of osmotic pressure to normal This author is very guarded in his conclusions and suggests that the fall in plasma proteins (and osmotic pressure) as well as the edema of nephrosis may be produced coincidentally by the primary metabolic disorder and not be etiologically related to one another He is much disturbed by some inconsistencies in the cases of acute nephritic edema, forgetting, apparently, that other factors (increased permeability of the capillaries, etc) play a rôle here in addition to the plasma proteins More data on the osmotic pressure of the serum proteins in nephrosis during the formation and recession of edema are desirable

b Albuminuria, low plasma albumin but high total plasma proteins, and absence of edema The one carefully studied case reported by Salvesen (121) is of great interest because it presents negative evidence of value to the problem of nephrotic edema in sharp contrast to all of the positive types of evidence hitherto developed in this review The patient, a man 63 years old, developed weakness and persistent heavy albuminuria, 15 to 25 grams of protein per liter (Esbach), after an attack of "influenza" When seen 4 months after the onset, the strength had returned, there had been no change in weight, *never any edema* and symptoms were absent The blood pressure was 88/55 mm Hg Renal function was entirely normal The urinary sediment

showed occasional erythrocytes, few leucocytes and hyaline casts. The 24 hour urinary protein output on two days, by Kjeldahl, was 7 56 and 13 3 grams with 56 6 and 20 0 per cent of globulin, respectively In view of the enormous loss of protein for months the absence of edema was remarkable and unintelligible until the plasma protein analyses apparently gave the explanation The total proteins (5 chemical analyses in a period of 4 months) varied between 8 97 and 10 73 grams per cent (normally 6 53 to 7.96 for men according to Salvesen (122)), the albumin between 1 69 and 2 56 (normally 3 95 to 5 24), the globulin between 7 10 and 8 32 (normally 1.96 to 3 16). In spite, therefore, of the very low $\frac{\text{albumin}}{\text{globulin}}$ ratios—0 23 to 0 36—the globulin fraction was so markedly elevated that the total protein osmotic pressure was always well above the edema level The patient continued to have albuminuria, but never developed edema He died of pneumonia 7 months after he was first seen by Salvesen but was, unfortunately, not autopsied Whether he had a true nephrosis or not makes no difference The important fact is the unusual hyperproteinemia, with marked globulin regeneration capable of compensating for persistent, severe proteinuria which, under ordinary clinical conditions, would inevitably have led to marked edema at some time during the course of the disease Incidentally, this case illustrates the great importance of fractional analysis of the plasma proteins instead of the simpler total protein estimation Further study of similar cases would be very important

c Protein content of transudates in nephrosis. Taken by and large, therefore, the clinical evidence for the sequence, albuminuria → low plasma proteins → reduced osmotic pressure of the plasma proteins → nephrotic edema is so overwhelming as scarcely to admit of any other interpretation than one of cause and effect This was expressed by ...er (102) in discussing the inconsistencies between the surface ten- ... the serum and edema If the above relationship is correct, ... fluid in nephrosis should be of very definite composition in ... content and there should be no need for assuming, ...sed permeability of the capillaries By "per- ... permeability to plasma proteins or other col- ... ter, electrolytes and other small diffusible

molecules is so rapid in both directions through the capillary wall that one cannot conceive of any factor so influencing the rate of passage in one direction only as to produce edema or disappearance of edema In fact, Krogh (103) has expressed the whole situation most definitely and incontrovertibly in this statement concerning a case of intracellular edema "They (the capillaries) can neither hinder nor accelerate the absorption of salt and water, both of which substances diffuse freely through the endothelium, whether it is normally or abnormally permeable" (to proteins) McLean (120) has emphasized the fact "that alteration in permeability, in the quantitative sense, affecting only the rate at which substances pass through the capillary walls, will not affect direction of transfer of fluid, and hence will not have any appreciable effect on volume conditions" Therefore, if there is a change in permeability—an increase qualitatively—the edema fluid of nephrosis should have a considerable protein content

There is unanimity of opinion at present that the transudates in nephrosis show a lower protein content than any other form of free fluid Starling (123) stated that the low protein content of renal edema fluid was evidence against Cohnheim's theory of the inflammatory origin of the edema The protein content may be so extremely low as to make one wonder about the possibility of its derivation from the subcutaneous tissues in which the edema fluid has collected Epstein (124) was one of the first to demonstrate, chemically, the difference between "nephritic" and other edema fluids Thus the protein content of subcutaneous edema fluid from 3 "nephritic" cases varied between 0 098 and 0 171 gram per cent, as compared with 0 100 to 0 462 gram per cent in "cardionephritic" cases Similarly, while the peritoneal fluid in cardiac failure had from 1 567 to 4 712 grams per cent of protein, in atrophic cirrhosis from 0 521 to 3 332, in "cardionephritis" from 3 123 to 3 702 grams per cent, that from a "nephritic" case (nephrotic type) contained only 0 285 grams per cent In the case of luetic nephrosis reported in 1910 by Javal (22) the ascitic fluid was analyzed on three occasions, giving a protein percentage of only 0 2 to 0 4 Javal commented on the low figures but did not attempt to explain them Volhard (20) stated that the transudate in nephrosis was "almost a physiological salt solution," with a protein content (Esbach) usually between 0 025 to 0 05 per cent, at the most 0 1 per

cent, and a total nitrogen content of 0 036 to 0 12 per cent Beckmann (125) made an extensive study of the protein content of various types of edema fluid, using, however, refractometric analysis In 4 acute and 2 chronic cases of glomerulonephritis the edema fluid showed 1 12 to 2 52 grams per cent of protein, in 13 cases of cardiac failure 0 22 to 1 82, and in 4 cases of nephrotic edema (2 nephrosis, 2 amyloidosis) 0 01 to 0 31, again extremely low figures (on repeated determinations) for the nephrotic group The high protein content of the edema fluid in acute nephritis suggested to Beckmann true increase in permeability due to toxic vascular damage On the other hand, the strikingly low protein figures in "tubular nephropathy"—generally 0 1 gram per cent or less—pointed, according to Beckmann, to a tissue disturbance Fodor and Fischer (97) carried out analyses on the edema fluids of some patients over a period of months, obtaining many figures. In two cases of acute nephritis the percentage of protein varied between 0 39 and 0 96 In 2 patients with "nephrotic" glomerulonephritis, 20 different analyses gave a protein percentage ranging between 0 03 and 0 14, with an average of 0 07 In one case of "genuine" nephrosis 6 analyses showed 0 02 to 0 15 grams per cent of protein, the average being 0 08 A "luetic nephrosis" had 0 09 grams per cent of protein in the subcutaneous edema fluid, a "tuberculous nephrosis" (amyloidosis?) 0 03 The grand average for nephrotic edema fluid was a protein content of 0 05 gram per cent—almost no protein at all It is unnecessary to give further details since all the results reported by others have been perfectly uniform The ascitic fluid usually shows more protein than does subcutaneous edema fluid and less than do pleural transudates, but the amount is practically always below 0 5 per cent Any higher concentration of protein should suggest the possibility of peritonitis, unless the analysis is carried out on fluid concentrated as to its protein content by recent profuse diuresis

Interesting results confirmatory of the low protein content have been reported in connection with the determination of the *colloid osmotic pressure of transudates* Schade and Claussen (104) noted that nephrotic edema fluid had virtually no measurable protein osmotic pressure and that it was actively absorbed through the dialytic membrane by the corresponding serum in spite of the low protein osmotic pressure of the latter Of course, the filtration pressure present in capillaries

was lacking in their osmometer They held that "*increased affinity" of the tissues for fluids could never draw water out of the blood in the presence of free edema fluid* because the latter, with its protein content lower than that of the plasma, could exert no attraction for plasma fluid and therefore would act as a buffer between the blood and tissues This "buffer action" of free edema fluid has been entirely overlooked by proponents of increased tissue affinity for water Should the tissues have sufficiently "increased affinity" for fluids, then there should be no free edema fluid When the osmotic pressure of the plasma proteins increases above the critical level, then edema disappears regardless of the hypothetical tissue affinity Free tissue fluid of any sort, according to Schade and Claussen, never has enough protein in it to develop a higher colloid osmotic pressure (or greater attraction for water) than the blood This evidence and more of its kind seems to dispose rather definitely of the recently revived theory of edema as due to increased tissue affinity for water (Aldrich and McClure (126)), a theory with many reincarnations, but still not based upon readily measurable and controllable phenomena

Iversen (127) stated that the protein osmotic pressure of edema fluid of the filtration type is never above 15 to 20 mm of water—a truly insignificant amount

d Low plasma proteins, non-albuminuric in origin, and edema of "nephrotic" type If the thesis that low plasma proteins are an important causal factor in nephrotic edema be correct, one should observe a similar filtration type of edema, with low protein content, in other clinical conditions associated with low plasma proteins even in the absence of albuminuria or any other evidence of renal disease In other words, whenever the formation of plasma proteins has been interfered with by malnutrition or other causes and the accessory factors for the occurrence of edema, such as adequate salt and water intake, are present, edema should develop This did occur strikingly in the so called "war," "hunger" or "famine" dropsy so widespread in 1916 and 1917 in Central Europe and elsewhere, particularly in prison camps and among the poorer classes of civilian population in regions threatened with starvation Thus, Nixon (128) remarked on the low plasma proteins in the absence of albuminuria, without giving actual figures Jansen (129), however, in an admirable metabolic study of

"war-edema," found serum proteins below 6 4 grams per cent in 30 determinations out of 40, some as low as 4 grams per cent The normal serum proteins were 6 5 to 8 5 grams per cent The edema fluid, analyzed in 3 cases, contained 0 038 to 0 063 gram per cent of protein—typical nephrotic edema fluid There was no albuminuria in this series and the low serum proteins were explained as part of the general undernutrition and tissue-starvation These patients ingested large quantities of salt and water, making ideal conditions for edema in the presence of decreased serum proteins, i e, decreased ability on the part of the plasma to draw fluids back from the tissues once it had been forced out by the excess of hydrostatic capillary pressure over the osmotic pressure of the plasma proteins Renal function was normal in these cases and there was no cardiac failure It must be stated at this point that Jansen did not relate the edema to the low serum proteins but built up a complicated calcium-lipoid-endocrine disturbance theory However, Maver (130) in an excellent review of the entire field of "nutritional edema," clinical and experimental, clearly stated the connection between the lack of protein food and edema

A closely related type of clinical edema was reported by Wolferth (131) as occurring in two patients who suffered from impaired intestinal absorption following abdominal operations and who developed a severe undernutrition The edema was nephrotic in type, unassociated with any cardiac or renal impairment There was no significant albuminuria, yet the plasma proteins were markedly decreased—3 3 and 4 0 grams per cent, respectively This author emphasized the rôle of the colloid osmotic pressure of the plasma in the absorption of tissue fluids by the capillaries and pointed out the good response of the clinical condition to increased intake of food and improved nutrition A great many similar cases could probably be found in the literature, especially in association with severe diarrheas

It is only one step farther from the above edemas, non-albuminuric in origin, to the cachectic and starvation edemas seen in a variety of clinical conditions, including obstructive lesions of the upper part of the alimentary tract, severe anemias, advanced malignancies, etc This was early emphasized by Maver (130) In most of these states the general emaciation is reflected in moderate reduction of the plasma

proteins, down to 5 grams per cent, in the more severe cases down to 3 5 grams per cent, and soft edema of dependent portions of the body becomes manifest, according to Peters, Wakeman and Eisenman (132) They conclude that the low plasma protein is "at least a contributory cause of cachectic and starvation edemas" In more recent work, Bruckman, D'Esopo and Peters (221) have pointed out that the serum albumin is essentially the only fraction affected in various types of malnutrition They correlated the serum albumin level with the state of general nutrition Bruckman and Peters (222) also could demonstrate a constant relationship between the presence of nutritional edema and a serum albumin content below 3 per cent It may be emphasized here that the chronic undernutrition of some cases of nephrosis is often the result of misguided dietary restrictions and in itself may aggravate the reduction of the plasma proteins begun by albuminuria, as has been pointed out by Peters and Bulger (133)

The edema occurring in the course of severe diabetes mellitus presents a complicated problem Falta (134), in discussing famine dropsy, drew an analogy between it and the sodium bicarbonate edema in diabetic patients and emphasized the fact that both types of edema were producible only on diets rich in salt In 1923, Falta (135) admitted the possibility of the development of sodium bicarbonate edema in some diabetics even on a low salt diet Here again, the patient studied fulfilled the requirements for nutritional edema—marked undernourishment and a high fluid intake Even during the edematous period the urine volume was never less than 2800 cc daily The importance of malnutrition, increased intake of water and the lack of oliguria in diabetic edema were clearly stressed by Wilder and Beeler (136) They related the condition to war-edema and considered inanition as the determining factor They pointed out the striking incidence of diabetic edema, with polyuria and increased chloride excretion, during the "starvation" period of diabetic management and the anti-edematous effect of an increased intake of food In one of their cases edema developed in the absence of sodium bicarbonate therapy, thus ruling out alkalosis as a sine qua non in diabetic edema Joslin (137), (138), attributed diabetic edema mainly to the combination of undernutrition plus an excessive intake of salt and water, but also indicated the accessory effect of alkalies and the temporary retention

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of water in the body as the result of rapid storage of carbohydrate in the form of glycogen. The last mentioned factor was used to explain the edema occurring during an oatmeal "cure" The plasma proteins were apparently not considered by the authors quoted above. Peters, Bulger and Eisenman (139) found reduced plasma proteins quite regularly in severe diabetes with chronic malnutrition, except during diabetic toxemia when concentration of the blood took place While these authors found low plasma proteins in association with diabetic edema, they did not establish a cause and effect relationship between the two phenomena but attributed both to the undernutrition. In a later paper, Peters, Bulger, Eisenman and Lee (140) ascribed diabetic edema chiefly to undernutrition, partly to the excessive hydration following upon the cessation of acidosis and its dehydrating action, partly also to the unusual sensitiveness of the undernourished diabetic to the hydrating effect of sodium bicarbonate They stated that edema occurred only in diabetics who presented tissue wastage as a result of inadequate diets Adequate diets brought about spontaneous disappearance of the edema

In view of the above facts, it becomes extremely difficult to evaluate the rôle of insulin as an edema-producing factor in diabetic patients Undernutrition, the recoil from dehydration, large salt and fluid intake, at times alkalies, all are acting simultaneously with insulin in the severe diabetic who develops a temporary edema On the other hand, it may well be, as suggested by Wilder (141) and Joslin (138) that the rapid storage of carbohydrate, under the influence of insulin, has a temporary hydropigenic effect This would represent a purely indirect effect and not a specific action of insulin on water balance in the body It must be remembered that retention of water as a result of the deposition of glycogen in the liver and muscles would produce primarily an intra-cellular edema and not the ordinary anasarca However, the less striking gains in weight could be accounted for on this basis

e Experimentally reduced plasma proteins and edema Starling (6) was the first to correlate the osmotic action of the plasma proteins with the absorption of edema artificially produced in the hind extremity of the dog Schade and Claussen (104) constructed an artificial capillary system in which they could vary at will either the hydrostatic

filtration pressure or the osmotic fluid attracting pressure of the proteins of the perfusing serum, or both In this way they could produce at will, increased filtration of fluid from the capillary outward, at points in the system where the hydrostatic pressure was higher than the protein osmotic pressure, or the reverse when the latter was in excess over the former, or a condition of dynamic equilibrium when the two mechanical forces were evenly balanced The above experiments, while suggestive of a direct experimental basis for the clinical correlation between low plasma proteins and edema, were rather artificial and unconvincing because whole, living organisms with all their processes for adaptation to changing conditions by internal regulation were not the subjects of experimentation

The first direct proof of the occurrence of edema in intact animals with low plasma proteins was reported by Leiter (142) in 1928 The *plasma proteins were reduced in dogs* for days or weeks by the method of *plasmaphoresis Adequate salt and water intake* was provided for Under these conditions *edema and ascites occurred regularly when the plasma proteins had been reduced to, and maintained at, about 3 grams per cent* When protein depletion stopped for only 24 to 48 hours the plasma proteins rapidly rose above the critical level and edema disappeared *In these dogs the regeneration of plasma proteins apparently* takes place fairly rapidly (224) Extremely *significant was the low protein content of the subcutaneous edema fluid, usually below 0 1 gram per cent*, often much less The ascitic fluid usually had less than 0 25 gram per cent of protein These figures correspond excellently to those for nephrotic edema fluid and in themselves distinguish this experimental edema from most previous forms in that they definitely rule out capillary damage or increased permeability (to protein) In short, since the protein content of the edema fluid was usually not any higher than that of normal cerebrospinal fluid, the burden of proof is on those who postulate changes in the capillary endothelium of whatever nature This experimental edema, non-cardiac and non-renal in origin, appearing in the course of continued loss of plasma proteins seemed to furnish the necessary link in the chain of clinical and experimental evidence accumulating since Starling's original brilliant contributions to the subject of fluid exchange in the body Barker and Kirk (223) later produced a similar edema in dogs independently

Closely related to the above edema is that occurring in mice subsisting upon a low protein diet Denton and Kohman (143) and Kohman (144) (145) have observed this in studies upon diets in which carrots formed the only source of protein This edema develops at the stage of emaciation and bears a striking resemblance to the "war-edema" discussed above Recently, Frisch, Mendel and Peters (146) have repeated the entire work on rats, confirmed it in all its details and enhanced its significance considerably by determinations of the serum proteins They found the proteins reduced from the normal 7 grams per cent to below 4 grams per cent when edema developed Since the low proteins here were produced not by active loss from the body (as in nephrosis or in Leiter's dogs) but by decreased formation due to inadequate supply of proteins in the diet, it is not surprising that edema took 8 to 14 weeks to appear, while Leiter (142) obtained edema in dogs in 4 to 5 days The addition of protein to the diets of the rats resulted in rapid disappearance of edema and the return of the serum proteins, and the animals as a whole, to normal conditions The authors stressed the importance of salt and water intake as accessory factors in the edema The work, like that of Kohman, was very well controlled in regard to total calories, carbohydrate and fats, vitamin content, mineral balance, etc No analyses are available as yet upon the protein content of the edema fluid, but the results are predictable from the pathogenesis of this type of edema

f Summary of evidence concerning nephrotic edema From the material presented above the following "aphorisms" may be gleaned

1 All cases of active nephrosis have significant proteinuria

2 During the active stage, all cases of nephrotic edema have low total plasma proteins, or low plasma albumin—hence, all have low protein osmotic pressure

3 Nephrotic edema may disappear spontaneously or be absent in spite of albuminuria and low plasma proteins when the $\frac{\text{albumin}}{\text{globulin}}$ ratio is high enough to give an osmotic pressure of the serum proteins above 20 cm of water (i e . above the normal capillary blood pressure)

4 Nephrotic edema is much more likely to yield to various diuretic measures when the plasma albumin is above, than when it is below, about 2 grams per cent

5 Nephrotic edema rarely persists any length of time after albuminuria has decreased markedly

6 The edema fluid in nephrosis, like that in "war-edema" and experimental protein depletion, is a low protein filtrate of the plasma, very much like cerebrospinal fluid, formed and disposed of by known mechanical forces and not involving the permeability of the capillaries in any way

7 Low plasma proteins whether produced by loss of protein in the urine, by deficient regeneration as a result of disease or lack of proper building stones in the food, or by the combination of the two, are in themselves capable of accounting for the chronicity of nephrotic edema on a purely mechanical basis

8 Low plasma proteins and low protein osmotic pressure are certainly not the only factors in nephrotic edema, but probably the most significant A case of active nephrosis with an entirely normal plasma protein picture has not been found in the literature

D Disturbances in lipoid metabolism

a Increased lipoids in blood and transudates in nephrosis At about the same time that Munk was developing his ideas on lipoid degeneration in the kidneys and doubly refracting urinary lipoid droplets, Javal (22) attempted by chemical analysis to explain the milky appearance of the serum and transudates in a case of luetic nephrosis Two interesting facts came out of this work (*a*) There was a marked increase in the ether-soluble material (lipoids) of the milky serum when the patient was edematous—27 to 33 grams per liter, as compared with only 3 95 grams per liter in the clear serum when there no longer was edema (*b*) There was surprisingly little ether-extractible material in the milky ascitic fluid—0 35 to 0 88 gram per liter The same held true for the urine These two facts, established by rather crude methods, have been repeatedly confirmed Javal explained the opalescence of the ascitic fluid on the basis of its lecithin content, which formed 75 per cent of the total ether extract, and emphasized the importance of lecithin in water emulsions as the chief cause of opalescence in body fluids He supported these claims by experiments on such mixtures

b Cholesterol and its esters in blood and transudates Using the

cholesterol content as an index of the change in total lipoids, Chauffard, Laroche and Grigaut (147) pointed out the tremendous increase of the serum cholesterol in 3 cases of nephritis with edema—300 to 800 mgm per 100 cc—as compared with the figures in 9 cases of nephritis with urea retention or uremia—135 to 290 mgm, and values of 110 to 160 mgm per 100 cc in 9 cases of cardiac edema The authors noted an inverse relationship between the degrees of urea retention and cholesterol increase Chauffard, Richet and Grigaut (148) compared the cholesterol content of serum and edema fluid in 2 cases of nephritic edema and 2 of cardiac edema The edema fluids contained only 1 5 to 5 mgm of cholesterol per 100 cc while the serum had 270 and 330 mgm in the nephritics and 130 and 110 mgm per 100 cc. in the cardiacs The authors concluded that cholesterol, unlike urea and chloride, behaved as a colloid, not passing through the capillary walls into the transudates This, incidentally, is another bit of evidence concerning "permeability" of the capillaries in edema

Numerous reports have been published since this early work, all agreeing upon the occurrence of high blood, serum or plasma cholesterol in nephrotic edema No attempt will be made to go into the enormous literature on this subject The authors quoted below have already reviewed the earlier publications Epstein and Rothschild (149) found the blood cholesterol as high as 1226 mgm per 100 cc in nephrosis, as low as 80 mgm in uremia They also confirmed the earlier work in regard to the very low cholesterol content of transudates and urines A most thorough study of the serum cholesterol in all types of renal disease was reported by Stepp (150) His normal values were 130 to 170 mgm per 100 cc In nephrotic glomerulonephritis, acute or chronic, the cholesterol was found increased (in one instance to 686 mgm per 100 cc) In 5 cases of nephrosis the amounts ranged from 160 to 1170 mgm, usually between 300 and 600 The lower figures occurred in patients with diuresis and decreased albuminuria Stepp stated that the blood cholesterol could be used as an index of the "nephrotischer Einschlag"

Beumer (151) using the Windaus method, found the serum cholesterol in normal children to vary between 100 and 160 mgm per 100 cc, in 6 cases of acute nephritis with edema between 120 and 240, and in 4 cases of "nephrotic" edema (including amyloidosis) between 220

and 690 mgm per 100 cc Hahn and Wolff (152) carried out an extensive study upon the cholesterol content of body fluids and confirmed the occurrence of hypercholesterolemia in "nephrotic" types of renal disease The free and esterified cholesterol in the blood were increased proportionately Schwarz and Kohn (99) observed high serum cholesterol in all "nephrotic" children during the edematous stages, the values ranging between 300 and 900 mgm per 100 cc In 3 cases of nephrosis, Hiller, Linder, Lundsgaard and Van Slyke (153) reported plasma cholesterols of 510 to 620 mgm per 100 cc Gardner and Gainsborough (154) (155) and Gainsborough (156) have carefully studied the distribution of cholesterol and its esters in the plasma with the Windaus method and confirmed the findings of other authors who have used less accurate, colorimetric methods A recent investigation by Maxwell (157), in which 30 cases of "chronic parenchymatous nephritis" were included, led to the conclusion that increased plasma cholesterol was always found in true "renal" edema Again, the edema fluids analyzed contained only traces of cholesterol, at the most 10 mgm per 100 cc Differences in methods account for some of the variation in the values given above

c Urinary cholesterol and effect of ingestion of cholesterol on the blood and urine The characteristic occurrence in the urine of doubly refracting lipoid droplets, containing cholesterol esters, would lead one to expect a considerable urinary cholesterol content in nephrosis Furthermore, in the presence of marked hypercholesterolemia, excretion of ingested cholesterol should be favored Actual analyses of the urine have given little support to these expectations The figures must be taken with reservation because of the technical difficulties in dealing with such low concentrations of cholesterol compounds as occur in the urine Epstein and Rothschild (149) indicated the very low cholesterol content of the urine in "chronic nephrosis" without giving actual values Hahn and Wolff (152) found a daily urinary output of cholesterol compounds amounting to 20 to 35 mgm in a patient whose serum contained between 420 and 680 mgm per 100 cc and no urinary cholesterol in an edema-free patient with serum cholesterol of 350 to 440 mgm per 100 cc The ingestion of 5 grams of cholesterol had no significant effect on either the blood or urinary cholesterol in these two patients with nephrosis However, since the

cholesterol was not given with oil some doubt as to its absorption is expressed by the authors In the feeding experiments of Gross (158), the ingestion of 5 to 10 grams of cholesterol or even of 200 grams of butter, by patients with "nephrotic" types of renal disease, led to an increase in the number of urinary doubly refracting lipoid droplets in 4 to 7 hours, while no effect was produced in patients with glomerular types of renal disease Unfortunately, no chemical analyses were carried out in this study, but in a latter review Gross (159) stated that in a patient with nephrosis the daily output of cholesterol (chiefly as esters) in the urine which was 120 mgm on a fat-free diet, was increased to 600 mgm on a lipoid-rich diet These enormous values have not been confirmed, however, and probably were due to technical errors Burger (160) criticized severely much of the work on cholesterol involving colorimetric methods and justly emphasized the inaccuracies inherent in analyzing cloudy or colored fluids With the Windaus digitonin method, no cholesterol was found in normal urines In a case of nephrosis accurately studied for 8 days, the urinary cholesterol output per day varied between 0 35 and 3 12 mgm, being entirely independent of the albuminuria, the cholesterol level in the blood, and the cholesterol intake in the diet Burger concluded that the *urinary lipoids were directly dependent upon the intensity of tubular desquamation* and that the plasma cholesterol in nephrosis did not pass out into the urine any more than it did in diabetic or cholemic hypercholesterolemia, in which the urine was free from cholesterol Gaál (225) expressed the same views Using the digitonin method, Gardner and Gainsborough (154) found the total cholesterol excretion in the urine to be 1 7 to 4 2 mgm per day in normal individuals as well as in a variety of diseases In 3 cases of "subacute parenchymatous nephritis" with high plasma cholesterol values, the daily urinary cholesterol output (all forms of cholesterol included) varied between 16 and 42 mgm These authors brought forward evidence in favor of the existence of a conjugated "ethereal" type of cholesterol compound in the urine This form of cholesterol was stated to constitute from 30 to 70 per cent of the total cholesterol present in the urine It is interesting that 90 per cent of the urinary free cholesterol and its esters, in the urine of one patient, was found in the protein fraction, while the "ethereal" cholesterol remained in the protein-free filtrate Gainsborough (156)

pointed out that much more cholesterol could be salted out with the globulin than with the albumin fraction of the urine, and correlated this with the relative "solubility" of cholesterol in the two protein fractions. The recent investigation by Wichert, Popeloff and Jakowlewa (161) represents a careful metabolic study in which the blood, urine and feces were analyzed for cholesterol on low and high cholesterol diets, the latter consisting of the addition to the diet of 2 grams of cholesterol in sun-flower oil for one day. In healthy individuals virtually no cholesterol was found in the urine and the feeding experiment led to no increased excretion and little or no effect upon the blood cholesterol. In patients with various diseases including hepatic disease and obstructive jaundice, the urinary cholesterol was extremely low, less than 1 mgm. in 24 hours, and it was unaffected by the absorption of ingested cholesterol. In 4 cases of "nephrotic" renal disease, however, the urinary cholesterol output during the control period was as high as 12 mgm., with a rough parallelism to the severity of the nephrotic syndrome and the amount of doubly refractile lipoid droplets. In these patients ingestion of cholesterol led to considerable increase in blood cholesterol and a 50 to 200 per cent increase in urinary cholesterol, the maximum effect occurring in 1 to 3 days. The highest excretion was about 34 mg. in a severe nephrosis. A somewhat similar, though much less striking, response occurred in some patients with hypertension. It is interesting to note that no relationship was found between the level of cholesterol in the blood and that in the urine, even in nephrosis. It is also obvious that in future investigations some differentiation must be made between true excretion of cholesterol compounds from the blood and merely increased desquamation of lipoid-filled cells from the renal tubules. The specificity of "lipoid degeneration" in nephrotic types of renal disease and the apparent absence of cholesterol excretion in other conditions associated with a high blood cholesterol level lend support to the idea of a renal cellular origin of the urinary cholesterol in nephrosis.

d. The cause of hypercholesterolemia (lipemia) in nephrosis. It was not unnatural for Epstein and Rothschild (149) to assume that the lipemia in nephrosis, like that in diabetes, was an instance of non-utilization of lipoids that were derived largely from the food but partly, also, from the break-down of tissues during undernutrition. They

claimed that the lipemia subsided when the patients were given a high protein, low carbohydrate and low fat diet This effect, however, was probably related to improvement in the general condition of the patient rather than to any specific action on lipoid metabolism, and was not obtained in the absence of the former Schwarz and Kohn (99) observed no effect upon the blood cholesterol from the use of high protein diets Many other investigators have had a similar experience Keith (162) noticed diminishing lipoidemia in patients with nephrotic edema receiving very high fat diets Epstein (95) later denied any effect of the fat content of the diet upon the lipoidemia but emphasized the primary nature of this disturbance in the blood, in contrast to the secondary position of the lipemia in diabetes mellitus. Mobilization of body fat and general tissue degeneration were thought to be factors The degree of hypercholesterolemia was considered an index of the severity of the nephrosis In 1926, Epstein (163) wrote of a reciprocal relationship between the cholesterol level in the blood and the rate of protein metabolism, based upon the earlier work of Epstein and Lande (164) in which hypothyroidism and nephrosis were compared More recently, this author (11) stressed the relationship between lipemia and low plasma proteins, basing his opinion upon bleeding experiments on rabbits by Fishberg (165) (166) in which an enormous lipemia developed as anemia and low plasma proteins appeared

The lack of dependence of a high blood cholesterol in "nephrosis" upon the lipoid content of the diet was illustrated by Beumer in 1921 (151) in studies upon a 7 year old child who had extensive bone tuberculosis and "nephrosis" (amyloid) The serum cholesterol was 690 mgm per 100 cc (Windaus method) during the edematous state, 552 to 688 mgm after edema had decreased on a dry diet and urea therapy, 640 mgm after 9 days on a diet rich in cholesterol, and remained unchanged on a subsequent low fat, high protein diet However, a spontaneous decrease in serum cholesterol to 333 mgm per 100 cc occurred later and was likewise uninfluenced by a lipoid-rich diet Beumer denied the existence of a true disturbance in lipoid metabolism in nephrosis and deprecated attempts to restrict the fat intake of such patients According to Burger (160) an alimentary hypercholesterolemia occurs normally in man after ingestion of 5 grams of cholesterol

in olive oil, reaching a maximum within 4 to 5 hours with rapid return to a normal level However, no permanent increase can be effected by diet because of rapid excretion of cholesterol in the bile and feces

A direct attack upon the question of the cause of the lipemia in nephrosis and nephrotic types of nephritis was first made systematically by Hiller, Linder, Lundsgaard and Van Slyke (153) Using the fat meal (1 gram of butter per kilogram of body weight) these authors found no difference from the normal response in regard to the effect of the meal on the total metabolism and the non protein respiratory quotient The same held true for the blood cholesterol, which showed no significant consistent change after the fat meal The blood lecithin increased about 10 per cent more in the nephrotic group than in the normals The maximum increase in fatty acids, while varying considerably in both groups, averaged about 45 per cent in the nephrotic group, nearly twice the normal increment In three cases of uncomplicated nephrosis the control or initial plasma cholesterol was 510 to 620 mgm per 100 cc, the plasma lecithin 425 to 430 mgm and the plasma fatty acids 950 to 1040 mgm per 100 cc The authors concluded that there was no disturbance in the actual combustion or oxidation of fat in renal disease, but probably *a disturbed mechanism for the transfer of fat from the blood to the tissue depots*, accounting for the lipemia This important conclusion has not been given adequate recognition in those theories of the pathogenesis of nephrosis that postulate a serious upset in lipoid metabolism

Ling and Liu (167) have reported an investigation on the plasma lipoids in nephrosis which tends to confirm the conclusions of Hiller, Linder, Lundsgaard and Van Slyke They studied the proportion of saturated fatty acids in the plasma, as determined by the iodine number of the liquid fatty acids In 4 cases with normal total plasma lipoids, the average iodine number of the liquid fatty acids was 157 In 5 cases of "nephrosis" with total plasma lipoids 2 to 3 times the normal values, the proportions of unsaponifiable lipoids and liquid fatty acids were normal but the iodine number for the latter was 59 to 87, indicating that the fatty acids in nephrosis were far more saturated than normally These data suggested to the authors an accelerated delivery of fat to the blood from the fat depots with a relative slowness of the liver to deal with (unsaturate) it Inci-

dentally, they found a similar condition in 5 diabetics without significant increase in total plasma lipoids If these results are confirmed there would be considerable evidence in favor of regarding the lipoidemia of nephrosis as a phenomenon secondary to undernutrition and not indicative of a primary metabolic disturbance In this connection may be mentioned the lipemia so readily produced in rabbits by repeated bleeding until anemia and low plasma proteins result (166) It is risky, however, to draw analogies between lipemia in rabbits and lipemia in an omnivorous animal like man, as Burger (160) has so well demonstrated Gainsborough (156) felt that the hypercholesterolemia of nephrosis could not be accounted for, after considering all the organs or systems involved in the normal metabolism of cholesterol

e Relation of hypercholesterolemia to other clinical features of nephrosis. There is general agreement among nearly all the authors quoted above that no direct relationship exists between the cholesterol in the blood on the one hand and the plasma proteins, the degree of edema, the degree of albuminuria, the protein or lipoid content of the diet, or the amount of doubly refracting lipoid in the urine on the other hand. In general, the blood cholesterol is higher during active, edematous states in nephrosis, tending to fall during remissions If the increased blood cholesterol reflects a decreased rate of removal of lipoids from the blood stream no parallelism with other changes need be expected The results of the feeding experiments of Wichert, Popeloff and Jakowlewa (161), referred to above, may readily be explained on the basis of a delayed removal from the blood of the excess cholesterol absorbed from the ingested test dose Fishberg (166) has suggested that the lipemia in nephrosis may be a compensatory process acting to raise the colloid osmotic pressure of the plasma She presents no direct evidence

f The "lipoid degeneration" of the kidneys and hypercholesterolemia When Munk (76) (3) (26) first established the morphologic basis of "lipoid nephrosis" he clearly distinguished the peculiar "lipoid degeneration" with its doubly refracting lipoid from all other types of degeneration in the kidneys and stressed the irreversibility of the process and the inevitable death of the involved cells The absence of anisotropic lipoids in autolyzing material in vitro seemed to Munk to necessitate the assumption of a necrobiosis, a slow death of cells in

the living body The absence of such anisotropic material in degenerating liver or heart muscle and even in kidneys with marked fatty changes secondary to general disease or poisoning, made the presence of "lipoid degeneration" seem all the more a specific, local renal process In 1916, Munk (4) had already adopted the term "lipoid nephrosis," admitted an unknown, rather than luetic etiology in many cases and spoke of the syndrome as a "constitutional disease," but made no reference to hypercholesterolemia and its possible relation to the changes in the kidney The same held true for Fahr (15) and Volhard (20) in 1918 Genck (36), however, attributed the lipoid deposits in the kidney to an infiltration into damaged tubular cells, with lipoidemia as a necessary factor This point of view was reiterated by Gross (158) who definitely discarded "lipoid degeneration" for "lipoid infiltration," occurring from the blood, and thus explained the increase in urinary anisotropic lipoids after feeding cholesterol to "nephrotic" patients Stepp (150) was inclined to consider the lipoid deposits in the kidney as the source of the lipemia in nephrosis but admitted some of the difficulties involved in this point of view In 1922, Fahr (53) unequivocally accepted hypercholesterolemia in nephrosis as an expression of a general tissue, or extra-renal, disturbance leading constantly to lipoid infiltration of the kidneys This view he expressed again in 1925 (61) with the additional statement that *lipoid infiltration occurred at the very beginning of nephrosis*, in contrast to the relatively late onset in glomerulonephritis and amyloid disease of the kidney Munk (26) in 1925 still held fast to "lipoid degeneration" as an irreversible process leading to death of the cell, but admitted the secondary nature of the lipoid deposition in the kidneys, assuming in addition to the hypercholesterolemia a change in the physicochemical status of the lipoids (i e, anisotropism) with precipitation of the excreted lipoids in the cells, where they acted as irritant, foreign bodies Lowenthal (10) also emphasized the secondary, infiltrative origin of the renal lipoid deposits, the kidney acting as an excretory organ for the excess of lipoids in the blood Epstein (11) considered the renal lipoid deposits as occurring relatively late in the disease and of entirely secondary importance According to Aschoff (19), in a recent address, the tubular lipoid deposits are brought about by reabsorption from a glomerular fluid containing increased lipoid material

Gainsborough (156) suggested that the loss of protein in the glomerular capillaries might sufficiently alter the solubility relationships between the plasma proteins and the cholesterols to favor deposition of the latter from the blood in the tubular capillaries On the whole, therefore, there is agreement upon the idea that hypercholesterolemia, as one factor at least, determines the deposition of doubly-refracting lipoids in the kidney in nephrosis, instead of the older view that the lipoid deposits in the kidney were the source of the lipemia However, Beumer (151) and Burger (160) still consider hypercholesterolemia as secondary to renal and other cellular degeneration in nephrosis Fishberg and Fishberg (226) found no lipoid infiltration in the kidneys of lipemic rabbits

g *Chemical nature of the renal doubly-refracting lipoids* The beautiful work of Adami and Aschoff (168) (169) (170) early indicated that while a number of lipoids possessed the property of double refraction, experimentally the most striking effects were obtained with salts of oleic acid and above all with *cholesterol esters* of this and other fatty acids Of all the compounds tested cholesterol esters had the unusual ability of giving rise to characteristic "fluid crystals," under proper conditions, in the tissues and in vitro This work led the way to Windaus' (171) direct chemical analyses upon kidneys with and without anisotropic lipoids He used his own brilliant digitonin method for determination of the free and esterfied cholesterol In 2 normal kidneys the free cholesterol was 0 52 and 0 735 gram, or 0 22 and 0 26 per cent (of total kidney weight) respectively, while the bound cholesterol (as esters) was 0 071 and 0 034 gram, or only 0 03 and 0 012 per cent (of total kidney weight) Hence, there was a very slight amount of cholesterol esters in the normal kidney In 3 cases of amyloid disease of the kidney with varying degrees of anisotropic lipoid deposition histologically, the free cholesterol varied between 0 84 and 1 12 grams, or 0 27 to 0 33 per cent, and the bound cholesterol between 0 28 and 2 199 grams, or 0 09 to 0 65 per cent Hence, with relatively little variation in the free cholesterol there was an enormous increase, as percentage of moist or dry weight, in the cholesterol esters, paralleling the histological findings Windaus thus proved beyond a doubt that the *"lipoid degeneration" was a true infiltration and not a lipoid phanerosis* Furthermore, he succeeded in isolating and identi-

fying cholesterin palmitate and cholesterin oleate, two esters which Aschoff found to give the polariscopic and staining reactions of the anisotropic lipoids in the kidney In short, the doubly refracting lipoids of the kidney proved to be mixtures of true cholesterol esters This confirmed Panzer's (172) pioneer and less refined work in which "protagon" was shown to be cholesterol esters, in the kidney

An exhaustive morphological and chemical study by Fex (81) confirmed the findings of Aschoff and Windaus completely, besides adding valuable analytical data in regard to the cholesterol and cholesterol ester content of various other organs in health and disease Fex warned against interpreting double refraction as due to cholesterol esters in tissues unless a specific criterion was fulfilled—fluid crystals with typical Maltese crosses appearing on cooling after preliminary warming, and remaining unchanged for some time at room temperatures without crystallizing out Staining reactions were indecisive True cholesterol esters were not found in the kidneys except in chronic renal disease such as glomerulonephritis and "amyloid nephrosis" The chemical analysis of normal kidneys gave results essentially similar to those of Windaus (171) The kidneys from 2 cases each of diabetes, pernicious anemia and cirrhosis of the liver also showed a normal percentage of cholesterol and cholesterol esters In 7 cases of glomerulonephritis the highest percentage of free cholesterol (of moist kidney weight) was 0 297 (normal), of esterified cholesterol 0 294 (ten times the highest normal) In 2 cases of amyloid nephrosis the free cholesterol was as high as 0 356 per cent and the esterified cholesterol 0 419 per cent of moist kidney weight In other words, while the free cholestrol varied little from the normal in these diseases, the bound cholesterol was increased about twenty fold in some kidneys That this was not an apparent change only was indicated by similar high percentages when the dry weights of the kidney were used as the basis for computation Interestingly enough, the livers of these cases showed no significant deviation from the normal cholesterol and cholesterol ester content, and no anisotropic lipoids morphologically The morphological and chemical estimates of the amount of cholesterol esters paralleled each other quite regularly in the kidneys, according to Fex, but not at all in the adrenals

h Low surface tension of the serum in nephrosis Clausen (108),

using the drop-weight method, found the surface tension of the serum uniformly low in "parenchymatous nephritis" or "nephrosis" in children He thought that albuminuria was directly correlated with the lowering of the surface tension, apparently confirming his theory that the substance responsible for the reduction in surface tension was able to increase the permeability of the capillaries While edema had originally (173) been explained on the same basis—increased capillary permeability—Clausen in this paper pointed out that there was a closer relationship between low serum proteins and edema There was always edema when the serum proteins fell below 5 grams per cent Low surface tension and low serum proteins did not always go together Thus, in 15 cases of "nephrosis," 6 had very low surface tension while the serum proteins varied between 4 and 8 grams per cent Using the du Nouy tensiometer, Leiter (102) confirmed the occurrence of low surface tension values for the serum in nephrosis and nephrotic glomerulonephritis but was unable to correlate these directly with the extent of edema, the gross appearance of the serum as to milkiness, or the level of the plasma proteins He felt, without any direct evidence, that the surface-active substance was somehow related to the increase in blood lipoids and probably an incident, rather than a causative factor, in the disease or its major symptoms No further evidence has been published to modify this view

E Decreased basal metabolism

Aub and DuBois in 1917 (174) reported, among others, 5 cases of "chronic parenchymatous nephritis" with basal metabolic rates varying from −40 per cent to +14 per cent, the lowest rate occurring in a patient with marked edema In only two of the cases was the rate above −10 per cent The authors assumed that undernutrition played some rôle in the low rates Epstein and Lande (164) made a comparative study of hypothyroidism and nephrosis with emphasis upon the occurrence in both of a high blood cholesterol in association with low basal metabolic rates The basal metabolism in 5 cases of nephrosis fell between −8 and −18 per cent The reduction was attributed to faulty protein metabolism, a view consistently adhered to by Epstein (163) (164) who later emphasized that nephrosis was only a relative hypothyroidism and advocated thyroid therapy as a

means of stimulating the utilization of protein in the body Epstein (163) found the basal metabolic rate between —10 and —22 per cent in 60 per cent of the cases, normal or above in 40 per cent This is very significant because it indicates that a low basal metabolic rate is not a necessary feature of nephrosis and forces a reconsideration of all theories involving decreased metabolism as an important element in pathogenesis Low basal metabolic rates of about the same extent as the above values have also been reported by Hiller, Linder, Lundsgaard and Van Slyke (153), Liu (175), Platt (176) and in most of the individual case reports on nephrosis It is difficult to draw any definite conclusions concerning the relation between low basal metabolism and nephrosis, in view of the prevalence of similar metabolic changes in a wide variety of conditions associated with undernutrition and prolonged confinement to bed It seems that with the available evidence the burden of proof is more on those who claim a primary position for the low basal metabolic rate in nephrosis than on those who feel that the low basal metabolic rate is an incident secondary to undernutrition, therapeutic diets, inactivity and possibly other factors On the whole, little has been added to the understanding of the nature of nephrosis by the demonstration of the moderately reduced basal metabolism

Tolerance to thyroid medication It was pointed out by Eppinger in 1917 (177) and more emphatically by Epstein in 1921 (27) that thyroid extract could be tolerated in large doses by some patients with nephrosis That this tolerance could assume rather enormous proportions was shown in a more recent paper by Epstein (163) who gave as much as 4 grams daily of desiccated thyroid without any particular toxic effects One patient received an average of 1 5 grams daily for five months, followed by intravenous injections of thyroxin totalling 137 mgm in 11 weeks, without any striking changes in the basal metabolic rate and without any signs of thyrotoxicosis whatsoever Large doses of thyroid have been used by Molnar (178), Campanacci (57), Liu (175) and others, ever since the enthusiastic claims of Eppinger (177) as to the diuretic effects of thyroid substance in renal and cardiac edemas Symptoms and signs of overdosage rarely develop and increases in the basal metabolic rate are not at all regular This suggests first of all that in spite of the decreased metabolic rates

of these patients there is no true hypothyroidism, secondly that a tolerance to thyroid is found in other edematous conditions than nephrosis, and finally that the problems of absorption, the rate of destruction or inhibition, and the rate of excretion of the active thyroid substance must be thoroughly investigated in view of the obvious differences in the response of the basal metabolism in true edematous states and myxedema In this connection, Platt (176) has recently failed to demonstrate any thyroxin (by the tadpole method) in the urine of a nephrotic patient who was taking 7 to 14 mgm of thyroxin daily, by mouth, for 50 days In spite of these enormous doses, the patient's basal metabolic rate at the end of the period was —35 per cent, and there had been no noteworthy changes in the clinical status

F General theories of pathogenesis

a The theories Only the more generally accepted theories or those of historical interest will be discussed here In dealing with speculations about a disease which, as Epstein (11) so aptly expressed it, "is a compromise between clinical medicine and pathology" the mixture of clinical and pathological points of view, while confusing at times, becomes a necessary matter. Regardless, however, of what is ultimately accepted as the essential morphological basis of nephrosis, the general clinical syndrome still remains to be explained and for this reason one finds pathologists venturing into difficult physiological domains and frankly admitting the inadequacy of the visible structural changes to account for the manifestations of the disease

Beginning with the study of "lipoid degeneration" in the kidneys after the pioneer and classical study by Kaiserling and Orgler (35), *Munk* (3) built up the clinical and pathological structure of what he considered a primary degenerative (tubular) renal disease (nephrosis), often associated with active lues In 1916 (4) he used the term "lipoid nephrosis," emphasized the constitutional or general character of the disease and stated that syphilis was the only known virus to produce it in pure form, although many cases were not luetic in origin The edema was extra-renal in origin according to Munk, and on this point there was, and still is, pretty general agreement Munk, however, attributed the edema to the increased hydration capacity of the altered colloids of the body, an explanation as insusceptible of disproof as it

is difficult to prove The opalescence of the serum and transudates was also blamed, and with more justice, upon physicochemical changes in the colloids The important point of this entire theory was the explanation of the major symptoms of nephrosis on the basis of a *general, metabolic disorder, with the organic renal process distinctly in a secondary rôle* Renal function tests were stated to be of minor significance "Nephrosis" was accepted as a justifiable contrast to "nephritis" in view of the purely degenerative renal changes in the former In 1925 Munk (26) again emphasized the general nature of the disease and related the anisotropic lipoid deposits in the kidney to the hypercholesterolemia and physicochemical changes in the circulating lipoids, while attributing the (primary) renal epithelial damage to the same agent, unknown, which brought about the lipemia, an expression of an underlying general disturbance *Albuminuria* was due to a shift of the plasma colloids toward the coarser euglobulin fraction, which was treated by the kidney as a *foreign "denatured" protein* Edema was caused by a decrease in the hydrophilic colloids, and their change to lyophilic colloids, in the serum and cells *Albuminuria and lipoiduria* were considered as *compensatory processes* to rid the body of undesirable excesses in the affected colloids More recently, Munk (179) has restated these views and unequivocally accepted nephrosis as a disease entity, not a local renal disease but one of the "Nierenbegleiterkrankungen"

Volhard in 1914 (2), in conjunction with Fahr, popularized the term "nephrosis" as the name for the general group of tubular degenerative nephropathies, in which "genuine" or "cryptogenic" nephrosis formed the important clinical sub-group characterized by edema and normal renal function The *extra-renal nature of the edema* was clearly deduced and elaborated upon in such irrefutable fashion by Volhard in 1918 (20) as to have become an axiom *Vascular damage*, due to some hypothetical capillary poison originating in the degenerating kidney tubules, was made *responsible for the edema* on the basis of *increased permeability* Albuminuria was readily explained as tubular in origin It is extremely interesting that Volhard raised the question of a possible primary metabolic disturbance with secondary albuminuria, renal changes, etc (Munk's views) but dismissed this idea on the ground that albuminuria and lipoid deposits in the kidney were absent

in "war-edema," which was undoubtedly a general metabolic disturbance He finally confessed ignorance of the true pathogenesis

Fahr, who deserves most of the credit for establishing *nephrosis as a pathological entity*, described glomerular changes as part of the picture in 1918 (15) but took issue outspokenly with Lohlein and others in denying any dependence of the typical nephrotic tubular changes upon those in the glomeruli In other words, there was no doubt in Fahr's mind that he was *not dealing with a mild glomerulonephritis.* Even in "amyloid nephrosis" there was no parallelism between the degree of tubular degeneration and the amount of amyloid in the glomeruli There was, however, a consistent *association between edema and renal anisotropic lipoid deposits* in the cases with amyloidosis Fahr believed that toxic factors rather than local nutritional or vascular disturbances (as in glomerulonephritis) were important in the hyaline droplet degeneration of the kidney The *albuminuria was tubular* in origin, due to increased permeability of the capillaries and the damaged epithelial cells The edema was extra-renal in its genesis, due to toxic vascular injury with increased permeability of the capillaries to salt and water *Nephrosis* was, therefore, *both a general and a renal disease* just as glomerulonephritis, with the difference that *none of the symptoms in nephrosis was due to renal insufficiency* In 1922, Fahr (53) attempted to correlate anatomically nephrosis, nephrotic glomerulonephritis and "amyloid nephrosis"—the three most common diseases with the nephrotic syndrome In the degenerative glomerular changes—"*glomerulonephrosis*"—occurring in all three, Fahr saw the renal expression of general damage to capillary endothelium which, in the rest of the body, manifested itself in edema and hypercholesterolemia, the latter leading secondarily to the anisotropic lipoid deposits in the kidney Edema was considered as an obligatory cardinal symptom in lipoid nephrosis, but only a facultative one in the other two nephrotic syndromes There was no relationship between edema and the glomerular amyloid infiltration but a fairly constant parallelism between edema and doubly refracting lipoid deposits in the kidney, suggesting that both were due to the same extra-renal disturbance A vicious circle resulted from the continued cholesterol infiltration into degenerated capillary walls in the kidney, leading to destruction of the glomerulus and the entire nephron in time In this

paper Fahr definitely concluded that the *extra-renal (general) disturbance was primary in lipoid nephrosis, secondary in nephrotic glomerulonephritis and "amyloid nephrosis"* The cause of this disturbance was, of course, unknown but presumably some capillary poison In 1925, Fahr (61) summarized again his views on nephrosis He now separated "lipoid nephrosis" completely from the other "simple" (anatomical) nephroses and postulated a *primary tubular degeneration* (hyaline droplet, etc) with *secondary lipoid infiltration*, the *result of the general metabolic disturbance*, followed in turn by secondary irreversible degeneration of the tubular epithelium In this respect, Fahr's views of the pathological process in the kidneys closely approximate Munk's ideas The glomerulonephrosis occurred relatively late and slowly led to disappearance, by atrophy, of the corresponding nephrons The lipemia brought to Fahr's mind the suggestion of abnormalities in the reticulo endothelial system and the subcutaneous tissues, but he hunted in vain for anatomical changes in the reticulo-endothelial system and in the skin capillaries The difficult problems of the original renal injury and the occurrence of tubular degeneration at times with lipoid deposits and clinical edema, at times without these, could not be solved, but of one thing Fahr was certain—that *in lipoid nephrosis the renal lipoid infiltration occurred at the very beginning of the disease* and hence was not secondary to long-standing renal changes The primary morphological, though not demonstrable, change in nephrosis, was *degeneration of the capillary endothelium* throughout the body

Aschoff (8) stated his grievances concerning the term "nephrosis" very fully in 1917, the chief objections being that the term meant something different to every famous clinician and that all the autopsy material he had examined presented the findings of a *"burnt-out" glomerulonephritis* He did give *"nephrosis"* credit for signifying a *syndrome* but preferred "nephrodystrophy" as far more correct on a philological and pathogenetic basis Ten years later, in an address at Guy's Hospital in honor of the memory of Richard Bright, Aschoff (19) was no longer so certain of the glomerulonephritic origin of all cases of nephrosis and actually defined "so called nephrosis" in the general sense as a renal disease of *tubular degenerative* type with Volhard's nephrosis as one of this group, now designated by Aschoff as

"*lipoid dystrophy of the kidney*" He assumed that the cause of this disease was some infective-toxic damage of the whole organism, causing increased permeability of the glomerular capillaries to plasma proteins and to lipoids which, being partly reabsorbed in the tubules, led to hyaline-droplet and lipoid deposits *Increased permeability of the cutaneous capillaries was the cause of the edema* Typical contractions of the kidneys did not occur In short, to Aschoff the visible renal changes were apparently highly passive and unimportant However, he virtually admitted the existence of pure nephrosis, although he had fought that idea vigorously for many years

It was peculiarly significant when *Lohlein* (68), the foremost authority on the pathology of glomerulonephritis in all its varied aspects, admitted the existence of kidneys showing marked tubular degeneration with *glomerular changes definitely not inflammatory* in origin Case 25, of his 1906 series was an instance, and so were some of Fahr's cases (glomerulonephrosis) Lohlein thus disagreed with Aschoff on that score, although he, too, felt that the *vast majority of clinical cases of supposed nephrosis turned out pathologically* to be forms of *subacute or chronic glomerulonephritis* He drew an analogy between lipoid nephrosis and "nephrosis gravidarum," the "kidney of pregnancy," which was also a non-inflammatory glomerular process While practically accepting the concept of nephrosis, Lohlein, in all consistency with his previous views on glomerulonephritis (67), considered the *tubular changes in nephrosis as purely secondary to the slight glomerular involvement*, a point of view pretty well demolished by Fahr

Of all the theories on nephrosis in the literature, the one evolved by *Epstein* is most unique in the originality of its underlying assumption, in the intrinsic consistency throughout the years of its evolution, in its close contact with demonstrable facts and especially in a more ready susceptibility to experimental proof or disproof of its individual elements than any of the theories hitherto discussed It also has the distinction of being the first theory of nephrosis founded largely on definite biochemical and physiological, rather than morphological or nosological, evidence This has stimulated a large amount of important biochemical and physicochemical work upon various aspects of renal disease Basing his views upon earlier work (91) (124) proving the low serum protein level and insignificant protein content of the

transudates in nephrotic edema, Epstein (5) in 1917 discarded other theories of nephrotic edema as inadequate or grossly in error and emphasized the adaptation of Starling's views on the rôle of the *colloid osmotic pressure* of the blood to the *problem of edema* in nephrosis The low $\frac{\text{albumin}}{\text{globulin}}$ ratio in the plasma was due to the constant loss of albumin in the urine The increase in plasma lipoids represented tissue starvation The decreased basal metabolic rate (93) was more evidence in favor of a *metabolic or nutritional disturbance* Epstein saw clearly that "chronic nephrosis" was not at all related, clinically or pathologically, to the various types of "acute nephrosis," and that "amyloid nephrosis" was also something different In 1921 (27) the concept of nephrosis as a general metabolic disturbance was extended to explain the *albuminuria* not upon the usual assumption of increased permeability of renal capillaries, but as *due to active excretion* of *qualitatively changed* (chemically, physically or biologically) *plasma proteins*—in short, Munk's point of view The *quantitative changes in the plasma proteins were entirely secondary* to *this loss of protein* in the urine The term *"diabetes albuminuricus"* was proposed, leaving the kidney as unimportant a role in nephrosis as in diabetes mellitus The qualitative change in the plasma proteins made their utilization by the body impossible and, as a result, the rate of metabolism decreased (164) and lipemia developed, as in hypothyroidism To Epstein (95), therefore, *nephrosis became a full-fledged metabolic disease*, with, however, *some renal deficiency*, the expected non-protein nitrogen retention in the blood being masked by the dilution of waste-products in the edema fluid At this time, 1922, the *increased cholesterol* was considered the *primary change in the blood*, a direct index of the severity of the metabolic disturbance of nutrition In 1926, Epstein definitely ascribed the *renal changes* in nephrosis to *secondary effects* of the protein and lipoid metabolic disturbances (see Aschoff's view above) and *reciprocally related the cholesterol in the blood to the rate of protein metabolism* *Nephrosis* was only a *relative hypothyroidism* in which protein utilization could be stimulated by thyroid extracts Finally, in 1928 Epstein (11) reviewed clearly his thoughts of 25 years on "so-called nephrosis," to him "diabetes albuminuricus" The albuminuria was stated to be the first symptom, chiefly tubular in origin be-

cause the urinary $\frac{\text{albumin}}{\text{globulin}}$ ratios were so high as to preclude increased glomerular permeability as the main cause of proteinuria The *qualitative changes* in the *plasma proteins, making them foreign and useless* to the body, were compared with those occurring in immunity, too fine to detect by present chemical methods yet easily distinguished from the normal proteins by the kidneys in their excretory capacity The clinical picture was the same in all three nephrotic syndromes because it was secondary to the loss of protein common to all Glomerulonephritis and amyloid disease were merely coincidental in the nephrotic syndrome.

The increased blood cholesterol so constant in the edematous stages was partly explained on a possible dysfunction of the thyroid or adrenals Edema occurred after the disease was well-established, with water retention preceding manifest edema by a long interval. The *underlying cause of the metabolic disturbance was entirely unknown,* the so-called causes as lues, tuberculosis, pregnancy and infections being only exciting factors The relation to hypothyroidism was not of a genetic type and there was *no evidence of true thyroid insufficiency in nephrosis* The characteristic *tubular changes* were said to be a *late and secondary occurrence*, the only evidence given being the casual mention by Jungmann (180) of a biopsy on the kidney of a patient with clinically active nephrosis which showed "no anatomical substrate," whereas the autopsy some time later gave the typical morphological picture of nephrosis

The remaining theories are essentially in agreement with, or slight modifications of, the ones discussed so far. Thus *Schlayer* (12) in 1918 developed the theory of *general vascular damage in nephrosis* (see Fahr's views above) to explain the edema and the delayed lactose excretion. In other words, nephrosis was the long-sought-for clinical counterpart of Schlayer's experimental "vascular nephritis," in spite of its tubular lesions The latter were considered secondary. In this way Schlayer explained the absence of the nephrotic syndrome in the tubular necrosis produced by various poisons, and its presence in amyloid disease (vascular) of the kidney The gap was said to be bridged between nephrosis and nephrotic glomerulonephritis, both perhaps due to the same toxin, with no renal inflammation occurring

in the former because of an altered reactivity—a "dyscrasia" (181) In 1926 Schlayer (182) again stressed the general aspects of nephrosis in contrast to the unimportant renal element

Kollert's theory in 1923 (98) began with *increased cellular disintegration*, which gave rise to *coarsely-dispersed lipoid-protein* bodies (hence the milky serum) and *increased plasma fibrinogen*, the latter causing albuminuria above a certain low threshold value for fibrinogen, especially if the kidneys were already damaged by local disease The lipemia was also attributed to increased cellular degeneration *Edema* was blamed upon the *increased hydrophilic capacity* of the coarsely-dispersed tissue colloids, with the plasma fibrinogen somehow worked into this scheme Kollert denied increased permeability of the capillaries as an explanation for the edema of nephrosis In 1926 Kollert (14) elaborated upon this theory to add tubular damage to the sequence of events and succeeded, to his own satisfaction at least, in apparently reconciling the conflicting theories of Volhard, Munk, Epstein, Aschoff and Lohlein by somehow including them all To emphasize the general metabolic disturbance he suggested the terminology of "lipoid nephrosis in (bei) glomerulonephritis," "lipoid nephrosis in degenerative nephropathy," etc

Lowenthal (10), in 1926, accepted Fahr's histological findings completely but added to them the occurrence of marked *atheromatosis in the aortas of young individuals with nephrosis* He thought there was a close *resemblance to the experimentally produced atheromatosis in rabbits* (by feeding cholesterol in oil) The renal tubular changes were stated to be not degenerative, in view of the preservation of the nuclei, but purely infiltrative Lipoid nephrosis was accorded the position of a unique clinical and pathological entity, with enormous *emphasis on the disturbed lipoid metabolism, for the anatomical seat of which the author searched in vain* in the liver, pancreas, gonads, kidneys, the gastrointestinal tract and the reticulo endothelial system of his autopsied cases The *kidney was merely an excretory organ* in nephrosis, as in Epstein's theory In 1928, Lowenthal (54) made another critical review of the literature on nephrosis, added more autopsy reports of his own carefully-studied material and came again to the conclusion that *lipoid nephrosis existed in a pure form* as an independent disease Lues played no role in any of his cases He could blame no one organ

for the disease but drew a close analogy with experimental hypercholesterolemia in lower animals, considering the lipoid metabolism as the keystone of nephrosis. His designation for the disease, à la Epstein, was "*diabetes lipoidoproteinicus*."

The English points of view on nephrosis were illustrated on the one hand by *Allbutt* (183) who, in 1918, discussed and apparently accepted Epstein's early theory, thus "turning from Galenism to biophysics." On the other hand, *Dunn* (184) felt that "nephrosis" was a sub-type of "subacute nephritis," the kidneys always revealing stigmata of *antecedent glomerulitis*, namely, small adhesions of the tuft to the capsule and fatty degeneration of the glomerular capillary endothelium—changes rather similar to those described by Fahr and even Lohlein as not necessarily inflammatory. *Bennett*, *Davies*, and *Dodds* (185), in 1927, gave a clear outline of the evolution of nephrosis, laying special emphasis on hypercholesterolemia and its relation to the renal lipoids and edema. They reviewed the existing theories, accepted extra-renal causes of edema, but left the decision open as to the theory they preferred. More recently, in the Goulstonian Lectures, *Bennett* (186) accepted "*nephrosis*" *as an entity* and showed a considerable willingness to let go of the traditional British classification of renal diseases. *Gainsborough* (156), however, refused to consider "*nephrosis*" as other than a *syndrome in glomerulo-tubular nephritis* and objected to the creation of another entity. He believed that the edema and the other metabolic disturbances might be explained on the basis of the changes in the composition of the plasma due to the albuminuria. Hence, the assumption of unknown, extra-renal factors became unnecessary.

In the United States, in addition to Epstein's theory, there have been published, among others, the views of Marriott and Clausen, Aldrich, Elwyn, Bell and Fishberg. *Marriott* (173) considered the "*acute parenchymatous* (*tubular*) *nephritis*" *of children* as identical with nephrosis. It was always secondary to infection, usually a *staphylococcus aureus maxillary sinusitis*, and removal of the infection by drainage of the sinuses resulted in rapid recovery regardless of the type of diet. The *edema* was *produced by increased capillary permeability*, in turn caused by the surface-tension lowering substance described by Clausen (108), apparently a product of staphylococcal action on the tissues. *Clausen* (108) combined this etiological classification with

emphasis on the *loss of body protein*, also secondary to increased permeability as a result of the action of the *surface-active substance* To these authors, therefore, nephrosis was a general systemic disorder caused by focal infection with the staphylococcus

Aldrich (31), while accepting the non-renal basis of nephrotic edema and the importance of infections as etiological factors, refused to limit the seat of infection to the nasal sinuses and the organism to the staphylococcus He suggested, among other possibilities, that *nephrotic edema* might be *due to an increased affinity on the part of the body cells toward water* Bacterial toxins were considered the cause of the change in affinity of the tissues for water The *edema* might be a *protective mechanism to dilute toxins* (187)

Elwyn (188) developed a *teleological theory* of nephrosis unique in its constitution To him nephrosis was not an independent disease but *always the result of an acute glomerulonephritis* or the toxin of amyloid disease In either case there were *persistent glomerular damage* and albuminuria and in response to the latter a *compensatory oliguria* and regeneration of plasma globulin *Edema then occurred*, in order *to prevent increase in blood volume* during the period of oliguria The edema, thus, was a sequel of purposeful renal retention of plasma proteins The edema fluid had little protein in it because the *universal capillary constriction* (as indicated by the pallor of patients) purposefully *prevented the loss of protein from the blood* However, this capillary constriction led to diminished tissue oxidation, hence the low basal metabolic rate and the accumulation of lipoids in the blood and tissues In 1929, Elwyn (189), in his book on edema, summarily dismissed the plasma proteins as of any real importance in edema of any sort but built up a hypothesis of *disturbed regulation* with especial emphasis upon the *hypothalamic centers*, the "hormone" pituitrin and peripheral "constellations of electrolytes" The *low plasma proteins* in nephrosis were now *attributed to decreased function of a special vegetative center* Vegetative centers and hormones kept the blood volume always constant In nephrosis there was always a primary glomerulitis which subsided anatomically but persisted as functional damage, accounting completely for the albuminuria

Bell (72) has very recently reviewed the status of nephrosis and, after the study of 4 cases of what he considered as "pure lipoid nephrosis"

and of several other cases of nephrotic glomerulonephritis, has come to the conclusion that "*lipoid nephrosis appears to be a renal lesion in which there is partial but not complete obstruction of the glomerular circulation*" by enlarged or proliferated endothelial cells or by thickening and contraction of the hyaline glomerular basement membrane, as demonstrated by McGregor's (73) method Transitions of all degrees could be found histologically between his cases of "pure lipoid nephrosis" and the obvious forms of glomerulonephritis However, the clinical absence of uremia in nephrosis was reflected in the statement that *contracted kidneys were never found in nephrosis* The tubular changes were attributed by Bell to the glomerular involvement

In a brief but lucid review of the nature of nephrosis, *Fishberg* (227) accepted without reservations the cause and effect relationship between albuminuria, diminished plasma proteins and edema He considered as established the existence of nephrosis in the absence of previous glomerulonephritis He was inclined to admit the possibility of both the primary renal and the primary metabolic origins, in which event the term nephrosis would "ultimately prove to be merely a collective concept embracing several distinct diseases, each characterized clinically by the consequences of loss of great quantities of protein in the urine and anatomically by purely degenerative lesions of the kidney"

Govaerts (213) assumed a primary toxic damage of the glomerular capillaries to explain the albuminuria His theory of the pathogenesis of nephrotic edema has already been discussed The lipoid infiltration of the kidneys in nephrosis was attributed to tubular reabsorption, as in Aschoff's theory The origin of the hypercholesterolemia was admitted to be entirely unknown, but undoubtedly extra-renal. As to the direct etiology of nephrosis, the possibility of chronic pneumococcal infection was suggested

b Critical considerations Criticism of the various theories outlined in the preceding section is attempted here chiefly for the sake of pointing out the weaknesses resulting from lack of sufficient factual background, and in the hope of stimulating future investigation of the major problems of nephrosis Theories are vitally necessary as ferments, but care must be taken that there be a proper relationship between the substrate of material facts and the amount of speculation

The essentially similar point of view of *Munk* and *Epstein* in regard to a qualitative change in the plasma proteins is an interesting hypothesis and one capable, in itself, of explaining most of the important features of nephrosis However, *one thing is lacking—evidence that such a change or denaturation of the proteins has actually taken place* It should be possible by some biological method, if not chemically, to demonstrate a difference in proteins which is discernible to the patient's kidneys Until some variation is discovered between normal plasma proteins and those of nephrotic patients, the theory of Munk and Epstein remains an uncertain speculation It may be interesting to refer again to the work of Hewitt (86), (87), who, on the basis of precise physical methods capable of detecting differences between purified proteins, was able to demonstrate the identity of serum and urinary proteins in various diseases, including nephrosis Furthermore, in several patients with marked Bence-Jones proteinuria observed for a number of years, no serum albumin was found in the urine at any time This fact, according to Hewitt, rendered untenable the theory of Thomas, Schlegel and Andrews (88) who postulated that albuminuria in renal disease was secondary to damage of the kidneys by a tissue protein foreign to the normal plasma and circulating in the blood early in nephritis

Whether Munk is correct in regard to the primary nature of the shift of the plasma proteins toward the globulin fraction, or Epstein is, in considering the increased globulin as purely secondary to increased rate of regeneration consequent upon loss of protein, remains for future study of the course of this change as correlated with the course of the disease from its beginning to its end On the whole there is much clinical and experimental evidence in favor of Epstein's idea

To *Epstein* the concept of a change in the permeability of the glomerular capillaries seemed to be insufficient to account for the high $\frac{\text{albumin}}{\text{globulin}}$ ratios Yet there is nothing seriously unintelligible in the view that there may be just enough change to allow the much smaller albumin molecules to escape while the larger globulin molecules remain Furthermore it is equally plausible that a further increase in permeability would allow more globulin to escape into the urine

and give lower $\frac{\text{albumin}}{\text{globulin}}$ ratios Finally some glomerular capillaries could be altered more than others, so that all proportions of albumin and globulin in the urine would be possible This state of affairs might account for the marked variations even in the same patient under fairly constant conditions, assuming that the technical methods are really reliable Obviously, there is room for much careful work on clinical material

The non-utilization of the plasma proteins and the consequent decrease in metabolic rate in nephrosis, as assumed by Epstein, have not been proven Since many patients with nephrosis do not exhibit a reduced basal metabolism, the supposed non-utilization of the protein, present in all cases, cannot therefore be the chief cause of the change in the energy metabolism But the most difficult point in Epstein's general theory is the understanding of how recovery or even temporary remissions can occur in a disease associated with serious biological alterations in the plasma proteins, unless for some reason normal plasma proteins again are formed and albuminuria, therefore, ceases There is no analogy of such a recovery in any other general metabolic disorder and there is certainly no logical explanation of the effects of a high protein diet, thyroid therapy or any other procedure, all of which would, in some way or another, not only have to stimulate the utilization of the plasma proteins but also cause the regenerative mechanism to begin building normal, non-excretable plasma proteins Since Epstein admits the inherent tendency of nephrosis to complete recovery when uncomplicated by other diseases, he must explain on the basis of his theory, the mechanism of recovery. This he has not done so far The disappearance of the nephrotic syndrome, as Epstein (11) himself emphasizes, in cases of glomerulonephritis which have proceeded to definite renal insufficiency cannot be explained on the theory of altered plasma proteins His explanation of the edema in nephrosis seems the best one available at present and by far his most important contribution to the entire subject of nephrosis Finally, the time relationship of the anatomical changes in the kidney to the active clinical syndrome still remains to be accurately determined On the best authority available (Fahr) it is quite different from that assumed by Epstein with only Jungmann's sketchy

statement about one patient as evidence Additional detailed pathological studies in Epstein's papers would render his published clinical experience more valuable than it now is

The theories of Volhard, Fahr, Aschoff, Schlayer, Marriott, Clausen, and others may be dismissed in so far as in all of the these the edema of nephrosis is explained on the basis of increased capillary permeability, an assumption pure and simple, readily disproved by the low protein content of the transudates and theoretically impossible even if by "permeability" is meant the ability of capillary walls to allow salt and water to pass through them The wrongness of this idea of "permeability" was clearly pointed out by McLean (120) in his recent review of the general problems of edema Where the theories of the above authors refer to increased permeability (to protein) of the glomerular or tubular capillaries, there is no criticism to offer It is interesting that the pathologists, Fahr and Aschoff, as well as the clinicians, assign a secondary role to the kidneys in nephrosis and accept the idea of a general, metabolic disturbance More striking, however, is the apparent limitation of the recognizable morphological changes to the kidneys *Fahr,* it seems, has definitely proved the occurrence of nephrosis, though rarely, as a pure disease entirely independent of any co-existing or preceding glomerulonephritis *Marriott and Clausen* have not distinguished clearly enough between cause and effect in regard to nephrosis and staphylococcal sinusitis, nor has their work been sufficiently confirmed by other pediatricians The relationship of their surface-active substance to edema and albuminuria is very vague and unsupported by adequate evidence

Kollert's theory involves an increased general cellular disintegration in nephrosis for which there is no foundation in fact Furthermore in clinical diseases definitely associated with marked tissue destruction—widespread tumor metastases, starvation, severe infectious diseases, acute yellow atrophy of the liver, etc —there is usually no serious albuminuria nor edema The very high plasma fibrinogen values in nephrosis were partly due to errors in the method of analysis, according to Kollert and Hartl (107) The causal relationship of high plasma fibrinogen to albuminuria has not been confirmed and does not hold in febrile hyperfibrinogenemia, according to the proponents of this theory Kollert's theory of edema as of cellular or tissue origin, has

the advantage of similar hypotheses in the literature in that it is not directly capable of disproof but is apparently convincing enough to many clinicians not to require any proof. The reconciliation or compounding of many different theories, each with its own assumptions and errors, as Kollert has attempted, does not offer any guarantee of greater truth in the resultant hypothesis The pathogenesis of nephrosis, therefore, has not been clarified to any significant extent by Kollert's theory

Elwyn's theory can only be criticized on the basis that its individual parts involve such highly teleological concepts as to make one wonder how such a beautifully self-regulating mechanism could ever be seriously disturbed by the slight glomerular damage he assumes as the primum movens in nephrosis His theory is logical in its structure if its numerous assumptions are granted In his zeal for "regulation," Elwyn loses sight of much simpler peripheral mechanisms in the body, and his theory of edema becomes literally top-heavy with vegetative centers

Lowenthal has attempted to line up nephrosis with other primary disturbances in lipoid metabolism, especially with the experimental hypercholesterolemias of rabbits Yet his own extremely careful pathological study of nephrosis pointed to one fact very clearly—that the organs or systems constantly affected in either the clinical (Gaucher's disease, Niemann-Pick's disease, xanthomatosis, diabetic lipemias) or experimental lipoid metabolic disturbances (in rabbits, particularly) were never appreciably involved in nephrosis *Shapiro* (52) while finding some doubly-refracting granules in the splenic follicles and lymph-nodes took pains to emphasize the *differences between nephrosis* and *the true diseases of the reticulo-endothelial system* *Schonheimer* (190) *and Lubarsch* (78) have emphasized *the absence of anisotropic lipoid infiltration of the renal tubular epithelium in experimental hypercholesterolemias* even though the entire reticulo-endothelial system and other organs were packed full *It is a long and dangerous step by analogy from experiments on the lipoid accumulations in a herbivorous animal, the rabbit*, notorious for its peculiar behavior in many other respects, *to a disease like nephrosis in an omnivorous animal, man*, particularly when *known diseases of lipoid metabolism in man produce neither the clinical nor pathological findings of nephrosis* The whole problem of

the origin of the hypercholesterolemia in nephrosis and its relation, in time and effects, to other features of the disease has scarcely been touched by controlled scientific investigation

Bell's theory would be extremely important if its author had observed for his own cases of "pure lipoid nephrosis" the criteria he justly laid down for the others in the literature That this was not entirely the case is indicated by the following facts Case 1 presented an acute onset, increasing anemia, increasing blood urea, low phthalein output (intravenous), death within 4 weeks after the onset Case 2, a child of 4 had an acute onset, a systolic blood-pressure ranging between 108 and 118 mm Hg, progressive anemia, considerable urea nitrogen retention in the blood and enough infection in the middle ear and sinuses to furnish an excellent focus for glomerulonephritis Cases 3 and 4 could scarcely be considered clinically as "pure lipoid nephrosis" The finding of histological changes differing only in degree from the ordinary types of glomerulonephritis was, therefore, to be expected in these cases and *Bell's conclusions regarding lipoid nephrosis were unwarranted insofar as he was not dealing with autopsy material of this disease* His conception of the dependence of tubular changes in nephrosis upon glomerular disease and the assumption of an incomplete obstruction of the glomerular circulation may be answered by Fahr's (61) unrefuted histological studies and the excellent renal function in nephrosis, respectively It must be added, however, that *the beautiful staining technic employed by Bell in these studies could profitably be used on all kidneys purporting to come from cases of uncomplicated nephrosis* It may turn out to be the best method for detecting mild or subsiding diffuse glomerulonephritis

NEPHROSIS, GLOMERULONEPHRITIS AND AMYLOID DISEASE

From what has been said above it is obvious that *uncomplicated nephrosis*, confirmed by autopsy findings, *is extremely rare* On the other hand, the *clinical syndrome*, in all of its details, *is vastly more common* All authors agree that mild glomerulonephritis and amyloid disease of the kidney may give a perfect duplicate of nephrosis clinically In view of the enormously higher incidence of glomerulonephritis than of nephrosis, it is natural that many experienced clinicians (Christian, for example (191)) have accepted the dictum of some pa-

thologists that pure nephrosis does not exist, or at least that its probability of occurrence at autopsy is so slight as to make it rash to diagnose a case as nephrosis All authors, however, admit the existence of the unique "nephrotic syndrome"

The nephrotic type of glomerulonephritis can mimic, down to the last detail, the entire clinical complex of the signs and symptoms of nephrosis There is not a single exception to this in the positive findings—albuminuria, cylindruria, edema, low plasma proteins, low $\frac{albumin}{globulin}$ ratios hypercholesterolemia, decreased basal metabolic rate, doubly refractile lipoids in the urine, normal renal function, low serum surface tension, etc As Friedrich Muller (9) pointed out years ago, the *differential diagnosis* of *nephrosis from glomerulonephritis is based* almost entirely *on negative* clinical and morphological criteria, since the positive criteria may be common to both *Distinction is possible pathologically,* although even the histological examination at times requires unusual skill and interest on the part of the pathologist in the interpretation of slight glomerular changes Clinically, the negative criteria—absence of cardiovascular changes, of gross or microscopic hematuria, of decreased renal function—are unfortunately not always present in glomerulonephritis at certain stages, or else slight changes may be overlooked, discounted, or be very difficult to interpret

This problem arose in the oft-quoted, painstakingly studied case of Mason (119) in which a typical clinical picture of nephrosis on the first examination was followed within less than a year by progressive anemia and decreasing renal function Microscopic hematuria for the first time was observed on 12 examinations 5 to 6 months before the patient's death, coincident with a maximum increase in edema, a blood urea nitrogen up to 39 mgm per 100 cc from a previously normal level and creatinine up to 3 6 mgm per 100 cc also from an entirely normal series of values However, because of the absence of increased arterial tension and other cardiovascular signs nephrosis was diagnosed, apparently on the assumption that the blood-pressure was always increased at every stage of every case of glomerulonephritis The reasonable diagnosis of an acute glomerulonephritis superimposed upon a previous nephrotic syndrome was not made by Mason, in spite of the fact that from then on the renal function rapidly

decreased The creatinine increased to 6 6 mgm per cent and the phthalein output in 2 hours never was above 10 per cent after that hematuric period The blood-pressure stayed low throughout, but the patient was Chinese, extremely undernourished and died of miliary pulmonary tuberculosis The autopsy showed kidneys weighing 115 grams together, with a finely granular surface and *glomeruli with "productive lesions"* in all stages No details were given as to crescent formation, anisotropic lipoid infiltration, etc Mason believed this was a classical case of nephrosis It seems to the reviewer that no such diagnosis was justified on the basis of the clinical course of the disease without the qualification that an acute glomerulonephritis superimposed itself on a possible nephrosis (probably a nephrotic glomerulonephritis) and led to rapid renal insufficiency and contraction of the kidneys *Glomerulonephritis can never be ruled out*, in spite of all claims to the contrary, *merely upon the absence of hypertension* and its consequences Even Volhard (20) recognized this difficulty in connection with "war nephritis"

Inadequate clinical differentiation is found also in the report by Kaufmann and Mason (70) in which one patient, aged 53, with hypertension, low phthalein output and high blood urea was classified as nephrosis clinically The paper by Labbe, Nepveux, Gilbert-Dreyfuss and Jung (228) describes a case of advanced glomerulonephritis as a "typical lipoid nephrosis" Complicating situations are also met with in the report by Zemp (192), and in some of Epstein's case reports (94) although this author recognized the occurrence of "mixed forms" —nephrosis with a later nephritis or vice versa—a rather weak classification because anatomically they must all be nephrotic types of glomerulonephritis, in which the time relationship of the supposedly independent nephrotic and nephritic components cannot be determined from examination of the kidneys Confusion between uncomplicated nephrosis and nephrotic glomerulonephritis clinically, to the discredit of the former at autopsy, is evident in Bell's (72) paper It is not uncommon in pediatric literature, as exemplified in the paper by Schwarz and Kohn (99), in which Case 8 began with hematuria which lasted for weeks, with a blood non-protein nitrogen up to 87 5 mg per cent and creatinine to 3 1 mgm, later returning to normal Their Case 11 also showed "hematuria on two or three occasions"

There were no autopsies in this series It is unfortunate that so little clinical or pathological detail is available in the large series of "nephrosis" in children reported by Marriott (173), Clausen (108) and Boyd (193) The loose use of "nephrosis" as a synonym for albuminuria plus edema and urinary doubly-refractile lipoids in utter disregard of the presence of cardiac hypertrophy, hypertension and other evidence of glomerulonephritis, explains the discrepancy between the clinical and pathological diagnoses in Cases 12 to 15 of the series reported by Stengel, Austin and Jonas (194) Gross misunderstanding of what "genuine nephrosis" means is evident in Bohnenkamp's (195) work

The inference to be drawn from these misconceptions is that the term "nephrosis" must be limited rigidly by clinicians to only those cases showing practically all of the positive criteria, and, what is much more important, all of the negative criteria at any stage of the disease Patients must be studied, more than ever, during infections when glomerulonephritis may flare up (see Longcope (196)) Diagnosis, therefore, can never be made at a single examination or even after months of careful study except on a tentative basis, and recovery of the patient does not necessarily rule out a nephrotic glomerulonephritis What can be usually diagnosed as Christian recently admitted (191), is the "nephrotic syndrome" but even this term should, properly speaking, be used only in the rigid sense defined for nephrosis and then clearly qualified by glomerulonephritis or some other diagnosis whenever possible Recently Shapiro (52) has claimed the possibility of differentiating clinically between pure nephrosis and nephrotic glomerulonephritis by the rapid removal of Congo red from the bloodstream and its early appearance in the urine, in the cases of pure nephrosis This finding is difficult to explain and requires confirmation There is only one criterion reliable in the diagnosis of uncomplicated nephrosis—histological absence of old or recent diffuse glomerulitis in the kidneys This criterion has been insufficiently employed by enthusiastic clinicians

In regard to "*amyloid nephrosis*," Munk, Fahr, Epstein and others now seem to regard the nephrotic component as a secondary occurrence in amyloidosis, although clinically it may for a time give the typical picture of nephrosis On the other hand, the underlying chronic disease is usually evident and helps to establish the diagnosis Some

cardiovascular involvement and renal insufficiency may develop in the older age groups (Fahr (15)), again ruling out an uncomplicated nephrosis Recovery is probably impossible, so that when it does occur in a patient with supposed "amyloid nephrosis" the original diagnosis must be seriously questioned Most, if not all of the cases of "nephrosis" reported as due to chronic tuberculosis are primarily amyloid disease of the kidney with secondary appearance of the nephrotic syndrome Anatomical amyloidosis often exists without nephrosis No case has been reported with amyloid in the kidneys in nephrosis of "unknown origin," that is, where one would ordinarily not have expected amyloidosis on general grounds There is no evidence that genuine nephrosis becomes an "amyloid nephrosis" in the course of time

NEPHROSIS, HYPOTHYROIDISM AND HYPOPARATHYROIDISM

The occurrence of considerable albuminuria in patients with true myxedema is not so rare but what a diagnosis of nephrosis may at times be made The presence of other classical signs and symptoms and the prompt response to small doses of thyroid preparations aid in the elimination of a wrong diagnosis of nephrosis This occurred in a patient of McIntosh (197) who, at first glance, seemed to be a case of nephrosis The difficulties are increased by the low basal metabolic rate and the hypercholesterolemia common to both Thus, Epstein (27) diagnosed the same patient as nephrosis in 1916 and classical myxedema in 1921 He wrote of the combination of nephrosis and myxedema in 1920 (94) That the two conditions may actually be combined in the same patient is strongly suggested by the case of Davidson (198) A man, aged 44, had definite clinical myxedema, marked edema and ascites, a basal metabolic rate of −32, albuminuria said to have preceded edema by 10 years, serum proteins down to 3 7 grams per cent, severe anemia and blood cholesterol of 309 mgm per cent On large doses of thyroid orally the weight dropped by 100 pounds through diuresis, and a normal metabolic rate was obtained The patient remained edema-free for some time, put on flesh but was still anemic He continued on 6 grains of thyroid daily A year later his basal metabolism was still normal, the symptoms of myxedema were absent but there was a constant tendency to edema, character-

however, has recently presented striking evidence to the contrary By allowing an adequate amount of protein in a high caloric diet it may be possible to promote the storage of food protein and presumably replace the protein lost in the urine, according to conclusions derived by Peters and Bulger (133) from recent extensive investigations upon the nitrogen metabolism in albuminuric, edematous patients With renal function normal in nephrosis in regard to excretion of nitrogenous waste-products, there is no need to worry about nitrogen retention in the blood on ordinary or even moderately elevated protein diets In fact, Epstein (5) purposely advocated a *high protein diet*, 150 to 200 grams daily, on the assumption that the general metabolism and protein utilization in the body would thereby be stimulated, even to the point of leading to a rapid increase in the plasma protein concentration, decrease in edema and recovery or a remission This rather unpalatable and difficult diet has not justified the original claims made for it, but its chief service has been in helping to erase the fear of meat, eggs, cheese and other protein-containing foods from the minds of some physicians and patients

c Edema The *edema*, of course, is the usual special object of therapy *Rest in bed* is absolutely essential when edema has reached a certain degree or is showing a tendency to increase. Rapid accumulations of abdominal or pleural fluid may be embarassing enough to the patient to require immediate *paracentesis* instead of diuretic drugs that require time and involve the element of chance Hydrotherapeutic measures, such as baths, sweats, etc , have not yet been shown to be sufficiently successful to offset the disadvantages of these methods *Restriction of salt and fluid intake* is of the greatest importance and when properly carried out may lead to successful diuresis, prevent further increase in edema and prolong the remissions once the patient has become edema-free, even though edema favoring factors, such as persistent albuminuria and low plasma proteins may still be present The rigidity of this restriction, however, as pointed out by many authors, must be guided by common sense and the general state of the patient It is better to have a well-nourished, slightly edematous patient than an edema free individual emaciated through loss of appetite During periods of severe edema the very strict *low-ionic diets* introduced by Keith, Barrier and Whelan (42) (43) and Keith, Smith

and Whelan (201), in which the total food water is only 800 to 900 cc, and the chloride less than 1 gram, seem to be indicated instead of the ordinary "salt-free" diets with their higher water, sodium and chloride content As soon as possible, however, the patient should be shifted to a less monotonous régime whenever a more palatable diet can be taken without causing a significant increase in edema Once vigorous diuresis sets in, and it may do so very suddenly, diet may make little difference *In young children the deprivation of water* may *effect too great a hardship* to warrant any strict low-fluid régime This fact and the feeling that children are more toxic when not enough water is given, have led Aldrich (34) and other pediatricians to allow water ad libitum or even to force fluids, apparently without harm

Many patients with nephrotic edema of considerable extent will respond relatively little to rest in bed and salt and fluid restriction, even when combined with paracentesis of the abdomen to decrease intra-abdominal pressure and the venous stasis in the large veins The use of *diuretics* becomes a serious problem The *purine* group ordinarily produce no effect other than unpleasant gastrointestinal upsets, in sharp contrast to their usefulness in cardiac edema *Potassium chloride* and other potassium salts may be excreted completely, in contrast to sodium salts, but the diuretic effect is usually insignificant In general, the *saline diuretics have little effect in nephrotic edema*

Urea was noted by Monakow (202) and others to have an excellent diuretic action in some patients with nephrotic edema Many have felt that a high protein diet, when effective, acts through the increased urea formation Urea must be given in large doses, 20 to 100 grams a day, and it apparently causes no difficulties other than gastrointestinal symptoms that may eventually require its discontinuance Since renal concentrating ability is normal in nephrosis, the excess urea is promptly excreted and only a moderate increase in blood urea betrays its use It has been given up to a total of several kilograms in a short period of time without any harmful effects The diuresis usually takes several days or a week to appear and is ordinarily moderate, ceasing when urea ingestion is discontinued In patients inured to the taste of concentrated solutions of urea, edema may be steadily cleared up by this drug However, it is a slow process Often urea fails completely, except for some increase in urinary volume with relatively little change in the weight of the patient

cases parathormone was ineffective in increasing the urine volume but a high protein diet and a fever, respectively, were successful in these patients Barker and O'Hare (206) were not particularly impressed with the effectiveness of parathyroid extract There have been no untoward effects ascribed to the parathormone in the above cases, all of which were carefully controlled by repeated serum calcium analyses

Removal of infection, by drainage and irrigation of the nasal sinuses, was recommended by Marriott (173) as more important than diet in leading to diuresis and possible recovery in children Davison and Salinger (55) obtained discouraging results on irrigating the antra in children Aldrich (31), however, reported prompt diuresis and loss of edema following the drainage of nasal abscesses and sometimes after the spontaneous improvement of colds. In this interesting paper Aldrich remarked that three children were apparently cured after severe streptococcal infections This *apparently beneficial action of infection* was strikingly evident in a girl of 16, reported by Karácsony (30). The patient's massive nephrotic edema had not yielded at all to the usual list—urea, digitalis, thyroid, novasurol, etc Then she developed lobar pneumonia, and novasurol given after the crisis was followed by rapid and complete disappearance of edema The edema returned three months later and remained obdurate to novasurol Lobar pneumonia again set in, there came another crisis and the patient's edema disappeared once more—in the absence of any medication Infection may be associated with increase or decrease in edema Epstein (11) considered the latter effect as due to increased protein metabolism. It is not at all uncommon for the terminal infection in nephrosis to be accompanied by rapid subsidence of edema Foreign protein therapy deserves investigation in this connection

The various diuretic measures described hitherto by no means exhaust the therapeutic armamentarium, but the very number and variety of these drugs and hormones indicate that the treatment of nephrotic edema is often a matter of hit or miss, and when a hit occurs chance and time may have been behind the scene In fact, one of the diagnostic features of nephrotic edema is its recalcitrance Equally characteristic is the tendency to sudden, overwhelming diuresis when the situation may look bleakest These facts should not dampen

[illegible]

The surgical removal of subcutaneous edema fluid is a therapeutic measure requiring no comment to establish its successful results. It is only in extreme cases, however, that one need resort to drainage of the edematous extremities by means of Southey's tubes. Cannulas are [illegible] or multiple incisions into the edematous skin. Drainage may be followed by diuresis due to improved circulation in the [illegible] veins. Strict asepsis must be practised throughout the entire procedure because of the great danger of [illegible] to be fatal in nephrosis. The [illegible] resulting from the [illegible] dietary restrictions in vogue some years ago undoubtedly played a role in the enormous dropsies met with by earlier investigators of [illegible] edema.

Artificial increase of the colloid osmotic pressure of the plasma by blood transfusion, infusion of gum acacia and similar substances has been suggested and tried without significant results. The theory is plausible enough but practical effects are bound to be disappointing because the amount of plasma protein or other colloid injected is hardly enough to produce a significant rise in colloid osmotic pressure in view of the limitations imposed by the capacity of the patient's circulatory system in regard to total plasma volume and also because *the glomerular capillaries are much more permeable than normally to colloids* (200) so that they do not remain long enough in the circulation. Epstein's theory that a high protein diet of itself led to rapid increase in plasma proteins has not been confirmed, and his own results can be interpreted in other ways. The plasma proteins eventually must be derived from amino

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therapeutic enthusiasm, but should stimulate scientific control and more work directed toward a better understanding of the fundamental nature of diuresis Volhard (20), Munk (26), Aldrich (31), Murphy and Warfield (29), Davison and Salinger (55), and other critical observers have not failed to notice and emphasize the striking independence often existing between the disappearance of edema and the use of a number of therapeutic measures It is therefore advisable, at times, to refrain from subjecting the edematous patient to one medicament after another in the vigorous attempt to promote diuresis The patient, and not the symptom, should be treated As Karger and Ullmann (60) have expressed it—"*Mit allzuviel Therapie wird hier nur geschadet*"

The *mechanical removal* of subcutaneous edema fluid is a therapeutic measure requiring no control to establish its successful results It is only in extreme cases, however, that one need resort to drainage of the edematous extremities by means of Southey's tubes, Curschmann cannulas or multiple incisions into the edematous skin Profuse drainage may be followed by diuresis, due to improved circulation in the decompressed veins *Strictest asepsis* must be practised, however, throughout the entire procedure because of the great *danger* of cellulitis, liable to be fatal in nephrosis The undernutrition resulting from the rigid dietary restrictions in vogue some years ago undoubtedly played a role in the enormous dropsies met with by earlier investigators of nephrotic edema

Artificial increase of the colloid osmotic pressure of the plasma by blood transfusion, infusion of gum acacia and similar substances has been suggested and tried without significant results The theory is plausible enough but practical effects are bound to be disappointing because the amount of plasma protein or other colloid injected is hardly enough to produce a significant rise in colloid osmotic pressure in view of the limitations imposed by the capacity of the patient's circulatory system in regard to total plasma volume, and also because *the glomerular capillaries are much more permeable than normally to colloids* (209), so that they do not remain long enough in the circulation Epstein's theory that a high protein diet of itself led to rapid increase in plasma proteins has not been confirmed, and his own results can be interpreted in other ways The plasma proteins eventually must be derived from amino-

acids present in food proteins, but the sequence of events in this process is entirely a matter of conjecture.

d *Miscellaneous.* There is no direct treatment for the lipemia nor any substantial evidence in favor of restricting the lipoid content of the diet as originally proposed by Epstein (149). The *complicating infections* in nephrosis, such as peritonitis or cellulitis, are to be treated along the usual, accepted lines with a full realization of the serious, though not completely hopeless, import of these infections Improved nutrition may help to decrease the susceptibility to infection of the transudates, and conservatism in regard to mechanical removal of fluids may reduce the possibility of contamination The edematous state of nephrosis is dangerous chiefly because the transudates form excellent culture media The usual source of the organisms is either the patient's own respiratory tract or the skin, hence, the predominance of pneumococci and streptococci as etiological agents (56)

Lues, when associated with the nephrotic syndrome should be treated, according to Munk (4) (26) (179), without any hesitation provided therapy is begun with iodides and mercurial inunctions After edema has subsided somewhat, small doses of salvarsan are to be given Munk has been consistently impressed with the almost specific effects of anti-luetic therapy in these cases. On the other hand, Burgerhout (24) considered the results uncertain and Epstein (11) flatly stated that anti-luetic measures brought about aggravation of the symptoms of nephrosis which responded very well, however, to the high protein diet and thyroid substance In view of this difference of opinion caution is warranted, and thorough study and publication of many more cases are indicated

Decapsulation has from time to time been advocated as a valuable method of therapy in patients with stubborn, nephrotic edema, usually on the theory that the kidneys themselves are also edematous and that the circulation within them is interfered with by the relatively non-elastic capsule In chronic, nephrotic edema, in contrast to acute glomerulonephritis and mercurial poisoning, there is no evidence of marked edema or increased tension within the kidneys, nor of impairment of glomerular circulation Therapeutic effects, therefore, are probably due to the operative partial denervation of the kidney or to the non-specific action of anesthesia, trauma, etc The circulation

of the renal cortex is probably not benefitted by the resulting perinephritic fibrosis. Horder (210) reported two cases of "subacute nephritis," nephrotic glomerulonephritis or nephrosis, in which immediate improvement followed decapsulation carried out during the chronic edematous stage. One case recovered completely within 6 weeks, edema having begun one and one-half years previously. This patient was examined four and one-half years after the operation and found to be perfectly normal. The author of this report admitted that he had no satisfactory explanation for the good effects observed following the decapsulation. In one of Oehlecker's (211) cases, striking improvement occurred within two weeks after decapsulation, but relapses followed and albuminuria persisted. This patient was in excellent health except for slight albuminuria, three years later. The surgical procedure was credited with bringing about a turn for the better, while nature did the rest. On the other hand, even this modest claim for the therapeutic efficiency of decapsulation may be counterbalanced by the unequivocal statement of Gainsborough (156) that "*decapsulation is quite useless*." The truth is probably not far from this.

SUMMARY AND CONCLUSIONS

The *nephrotic syndrome* seems to be well established clinically and pathologically as something not directly related to glomerulonephritis or inflammatory renal disease, although commonly associated with it. In its *primary, uncomplicated form, this syndrome is known as nephrosis* and is *a rare disease*. *The rarity of this disease*, however, is *no justification for the denial of its existence*.

The specific changes found in the kidneys in nephrosis and the absence of changes in other organs or systems suggest a *primary renal lesion*. Before one can accept such an hypothesis, however, it must be definitely established that the renal changes occur very early in the disease.

The view that nephrosis is a *general metabolic disorder*, with secondary involvement of the kidneys, is, likewise, not supported by sufficient evidence. There is lacking an adequate knowledge of the natural history of the disease. It is significant that there are no true metabolic diseases that tend toward spontaneous recovery as does

nephrosis Furthermore, such a theory offers no reasonable explanation for the frequent association of the nephrotic syndrome with glomerulonephritis and amyloid disease of the kidney The organic seat of this assumed metabolic derangement has not been demonstrated

In spite of the marked *increase in the blood lipoids*, particularly cholesterol and its esters, and the lipoid infiltration in the kidneys there is *no satisfactory evidence to warrant the inclusion of nephrosis* and the nephrotic syndrome *among the primary general disturbances of lipoid metabolism* The accepted diseases of lipoid metabolism are not associated with significant cholesterol ester infiltration of the kidneys Clinically, they bear no resemblance to the nephrotic syndrome It is possible that the constant loss of large amounts of plasma protein may secondarily lead to the lipemia and its consequences This, however, is mere speculation and critical observation and experimentation are needed before any definite conclusion can be drawn

The *albuminuria* in nephrosis may be explained in two ways On the one hand, a primary renal lesion may alter renal capillary permeability to the plasma proteins The experimental production of massive albuminuria becomes an important task for the investigator in this field Direct depletion of the plasma proteins by plasmapheresis is only a crude substitute On the other hand, the albuminuria may be secondary to qualitative changes in the plasma proteins and be a part of a primary metabolic disorder It should be possible biologically to establish the identity or non-identity of the plasma and urinary proteins in nephrosis with the proteins in the plasma of normal individuals

The *edema* in nephrosis is probably closely related to the reduction in the plasma proteins, whether due to renal loss or disturbance in formation On this feature of the disease there exists considerable evidence Through the common factors of low plasma proteins and edema, nephrosis and a variety of nutritional edemas, clinical or experimental in origin, are brought into more or less close contact It becomes all the more necessary, however, to acquire further information concerning the site of formation of the plasma proteins, their role in metabolism apart from osmotic effects, and the relationship between the plasma proteins and the lipoids

No condition has yet been produced in laboratory animals that could be dignified by the term "*experimental nephrosis*"

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THE SIGNIFICANCE OF LOCAL FACTORS FOR ELECTIVITY IN CENTRAL NERVOUS SYSTEM DISEASE PROCESSES[1]

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When we pathologists try to interpret our microscopic pictures, we are confronted with the problem of explaining the process which causes the localization and spread of special pathological lesions. This question, which plays a rôle in all bodily organs, has a very special interest in the central nervous system because of its special anatomy and the variety of localization of its disease processes. Where the changes are widespread and more or less equally distributed the question of localizing factors is not nearly so important as in diseases with specific anatomical localizations.

We see that even in general diffuse spreading there are special localities where the process is most active and others that remain strikingly free. In dementia paralytica, as has long been known, there is a contrast between frontal and occipital lobe, in general the lesions are quite diffuse, an atypical localization can predominate in place of the typical spreading. In contrast to this are the diseases that usually possess a striking equality in spreading as, for instance, amaurotic family idiocy in which one always speaks of the "ubiquitous" ganglion cell disease. But, even in this process, an especial section of the central nervous system may occasionally be involved, for instance the cerebellum in the late infantile form (Bielschowsky (1)). Certain well known nervous diseases have pronounced systemic types of degeneration, such as spinal muscular atrophy, amyotrophic lateral sclerosis, the elective cerebellar diseases, as well as some recently described processes in the extrapyramidal motor system. We recognize elective diseases of especial gray nuclei not only in the case of endogenous but also of exogenous destructive agents, for instance, the nucleus dentatus and the

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olive, in toxic conditions and diseases of infectious origin As regards the cerebral cortex, it is an old experience that the third layer is more vulnerable than all the others This is true of the most varied endogenous and exogenous processes, for example, pure degeneration, inflammation, and vascular diseases

In general we see that the system-disease processes stand at one end of a series while at the other end we find the diffuse disease processes In the center of this series are other processes which on the one hand accentuate the system-disease and on the other the diffuse changes The system-diseases show in the most striking manner the weakness of especial parts of the central nervous system against special destructive agents, as for example, the affinity of certain poisons for circumscribed areas and for certain anatomico-physiological organs in the nervous system

What kind of factors are these that determine the special localization of disease processes? These localized changes are interesting not only from the diagnostic, but also from the general pathologic and pathogenetic standpoint This question belongs to the general problem which is so much discussed today of *local vulnerability* and its causes Why have certain processes a special predilection or indeed a local electivity? What determines the point of attack of destructive processes? Why are certain parts of the central nervous system especially susceptible?

The histopathologic, but more especially the pathogenetic analysis of locally circumscribed lesions teaches us, according to my ideas, their *different* origins The electivity, with which many processes in the brain localize, can not be explained on a uniform basis My studies, which in part have been made with collaborators, show that the restriction of diseases to certain central regions originates under varying conditions, that the vulnerability can have many very different causes (2) The factors determining the locality are manifold indeed· some known and some as yet unknown, some simple and some complex The factors known today which to me seem the most important are the *systemic* and the *vascular* (or *vasomotor*) factors Spinal fluid is a further factor determining the local electivity Other types of vulnerability are as yet not sharply defined

First let us consider the *systemic* factors The neurological nomenclature already shows the rôle played by the system type in the pathol-

ogy of the nervous system For a long time we have been naming quite a number of nervous diseases after the affected system, some of which I have already mentioned In each case we have to do with a disease of one or more physiologically related systems

The fact that some of these processes attack anatomical systems, belonging together functionally, is so important that—to my mind—it seems to force us to continue using the old concept of "system disease" Some authors completely deny the existence of system disease However, we must urge counter reasons, from the standpoint of the pathological anatomist The pathologist is forced to admit the existence of real and independent system diseases, not only for clinical and pathological reasons, but also as the result of study of his anatomical preparations Diffuse destructions become of secondary importance, when contrasted with the lesions involving certain fibre tract systems and gray nuclei This proves that an *independent* disease of one or several functionally related systems can exist with accompanying but unimportant degenerations Above all, the diseases of the motor system should be mentioned in this category, as the French have done about the middle of the last century As a rather rare example, I wish to mention spastic spinal paralysis, because the existence of an independent spastic spinal paralysis is often denied, whereas spinal muscular atrophy and the amyotrophic lateral sclerosis are still acknowledged

I myself should even like to consider tabes dorsalis among the "system diseases" To my mind this also is a case of an independent degenerative process of an especial system dominating the disease picture I do not believe that one can recognize in tabes only a secondary degeneration caused by a syphilitic lesion of the extraspinal nerve roots as some other investigators do Examinations of beginning cases of tabes and comparative analysis of anatomical findings, have convinced me that here also the degeneration is systemic (3) In two cases of beginning tabes I noted the commencement of degeneration only from that point at which the posterior roots penetrate the spinal cord and where the nervous tissue adopts a central character In figure 1 is shown part of the posterior column with the posterior roots in a slide stained with sudan for fat The degenerating root fibers contain cells filled with fat, which clearly begin at the point where the posterior roots penetrate the spinal cord in the globoid portion (fig 1)

[illegible] being on the [illegible]

[illegible]

[illegible] detailed [illegible]

by the nature [illegible]

every way to [illegible]

[illegible]

circulation [illegible]

phine poisoning would look just the same This shows what I call "paling" ("Erbleichung") and this paleness is a characteristic of fresh necrobiosis in Nissl-preparations

Here and in various other conditions we often find simultaneous changes in quite a different part of the brain, namely in the Ammonshorn. In a former paper (12) I demonstrated their different appearance according to age Through different phases we could follow the process from the first paling till the end stage of a shrunken and scarred atrophy These findings show that the destroyed fresh necrotic or old scarred sclerotic part of the Ammonshorn is always in the same place, namely at the curve towards the ventricle, in the so-called "Sommer's sector" According to our researches, this is the typical expression of a disturbance in the circulation The latter may be organic as well as functional It may be caused by coarse material as an embolus or a thrombosis, or disease of the vessel wall, for instance, an endarteritis syphilitica or tuberculosa It can happen, however, that quite similar destructions appear at the same place, without a demonstrable occlusion of the circulation, so that we must suppose functional vasomotor disturbances Such pictures are seen in some cases of poisoning and infection and especially in epilepsies (13)

As a further example of the vascular type, I may name certain significant changes of the cerebellum These pictures will at the time demonstrate how difficult it often is to differentiate between a vascular and a systemic lesion In a fresh stage they are characterized by a branch-like connected proliferation of the glia cells These are nowadays called "Hortega cells," they have the characteristic rod form described by Nissl 30 years ago When I found them for the first time in cases of typhoid and typhus, I believed to have before me an elective disease of the Purkinje neurone (14) Indeed, one often sees how similar the connected glia cell proliferation is to the spreading of a Purkinje cell and its branches But then I noted the same thing in a circulatory disturbance from purely organic causes, and today I am of the opinion that this is another example of the vascular type of vulnerability Even where we have no material support for supposing circulation disturbances, the local lesion is exactly the same as in cases of definitely proven material occlusion of circulation Often the changes cover an area reaching only to the Purkinje cells, but the cases are not rare

in which the destruction and secondary glia proliferation ı the molecular zone into the granular cell layer The that evident, material vessel-lumen occlusions can produc quite analogous to those of the epileptic status and also like of some infections in which changes of the vessel wall and are lacking These examples suffice to illustrate the v of vulnerability

What is then the nature of these vascular factors in cert elective changes? In the case of elective diseases of certain we spoke with Ehrlich of the qualities lying in the tissues, of terior poison affinity Thus far these are really only words pa ing facts, and it is about the same thing if we speak of "*peculia* of the local circulatory conditions in cases of the vascular type

Many studies have been made to throw light on these peculi One is led to believe that very different factors may play a role, so times one, sometimes another factor, or sometimes a combination of th The vascular factors in question could lie in the greater or lesser d sity of the vascular network, or in the special arrangement of its mesh or in the form (Cerletti (15)), the quality and quantity of conn tions between the respective nutritive fields and neighboring ves the lack or abundance of tributaries from various vessel branches, t course, the angle of branching, and the direction of the stream St many another peculiarity may be of importance here

According to Uchimura's (16) and my own investigations, (17) th position and course of the main vessel in the attacked area and the la of tributaries are very important in the case of the Ammonshorn For the artery supplying the vulnerable sector of the Ammonshorn runs for a long stretch quite isolated in the septum The area supplied by this artery receives no tributaries in the form of other small arteries or arterioles This is in contrast to a certain part of the upper band of ganglion cells which is regularly spared The latter is supplied by various small arteries and receives its blood from several sources, whereas the sector is dependent upon a single vessel One can imagine that, in the case of functional or gross organic destructions which do not entirely interrupt the blood supply, the area supplied by only one artery has a disadvantage as compared to an area supplied by the tributaries of several arteries